Mayo Clinic Gastroenterology and Hepatology Board Review

Fifth Edition

Stephen C. Hauser

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To the many persons who have taught, encouraged, and inspired us so that we can provide the best care for our patients and help educate our colleagues to do the same.

Preface

Gastroenterology and hepatology encompass a vast anatomical assortment of organs that have diverse structure and function and potentially are afflicted by a multiplicity of disease processes. We have designed the Mayo Clinic Gastroenterology and Hepatology Board Review course and the revised fifth edition of this book to assist both physicians-in-training who are preparing for the gastroenterology board examination and the increasing number of gastroenterologists awaiting recertification. *Mayo Clinic Gastroenterology and Hepatology Board Review* is not intended to replace the many more encyclopedic textbooks of gastroenterology, hepatology, pathology, endoscopy, nutrition, and radiology now available. Nor is this book intended to serve as an "update" to physicians looking for the newest advances in the science and art of gastroenterology and hepatology. Instead, this book provides a core of essential knowledge in gastroenterology, hepatology, and integral related areas of pathology, endoscopy, nutrition, and radiology. Clinical knowledge related to diagnostic and therapeutic approaches to patient management is emphasized. Case-based presentations and short board examination–type, single-best-answer multiple-choice questions with annotated answers are featured. The text is also intended to be used by medical students and residents during their clerkships in internal medicine and gastroenterology and by gastroenterology fellows in training. Physicians in practice should find this book to be a practical review for consolidating their knowledge in gastroenterology.

The book is organized by subspecialty topics, including esophageal disorders, gastroduodenal disorders, small-bowel disease and nutrition, colonic disorders, pancreaticobiliary disease, liver disease, and miscellaneous disorders. Numerous color and black-and-white figures support the text. Each subspecialty section concludes with a set of board examination–type, single-best-answer multiple-choice questions with annotated answers. (The content of the questions and answers is not included in the index.) The faculty responsible for the book (at the time it was produced) all are Mayo Clinic gastroenterologists and hepatologists who spend the majority of their time caring for patients but have a commitment to teaching medical students, house officers, fellows, nurses, and physicians. Most of the faculty have particular interests in subspecialty areas of clinical gastroenterology and hepatology, which provides broad expertise.

We want to thank the staffs of Scientific Publications and Media Support Services at Mayo Clinic and the Mayo School of Continuous Professional Development for their contributions. The support of Mayo Clinic Scientific Press and our publisher, Oxford University Press, are also greatly appreciated. We want to give special thanks to our secretaries and to Vijay H. Shah, MD, for his ongoing enthusiasm and support for our faculty and teaching mission.

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I

Esophagus

1

Gastroesophageal Reflux Disease[a]

JOSEPH A. MURRAY, MD

Gastroesophageal reflux is the reflux of gastric contents other than air into or through the esophagus. *Gastroesophageal reflux disease* (GERD) refers to reflux that produces frequent symptoms or results in damage or dysfunction to the esophageal mucosa or contiguous organs of the upper aerodigestive system and occasionally the lower respiratory tract.

Etiology

Gastroesophageal reflux results from several factors that lead to symptoms or injury of the mucosa of the esophagus or the airway by reflux of corrosive material from the stomach (Box 1.1). These factors include a weak or defective sphincter, transient lower esophageal sphincter relaxations (TLESRs), hiatal hernia, poor acid clearance from the esophagus, diminished salivary flow, reduced mucosal resistance to injury, increased acid production, delayed gastric emptying of solids, and obstructive sleep apnea (Figure 1.1). The relative contribution of these varies from patient to patient.

Factors Contributing to GERD

Barrier Function of the Lower Esophageal Sphincter

The lower esophageal sphincter and its attached structures form a barrier to reflux of material across the esophagogastric junction and are the central protection against pathologic reflux of gastric contents into the esophagus. This barrier has several components, including the smooth muscle lower esophageal sphincter, the gastric sling fibers, and the striated muscle crural diaphragm. The lower esophageal sphincter maintains tone at rest and relaxes with swallowing and gastric distention as a venting reflex. This relaxation is TLESR. In persons with mild reflux disease, acid liquid contents instead of air alone are vented, resulting in many episodes of acid reflux. In patients with severe reflux, the resting pressure of the lower esophageal sphincter usually is diminished and easily overcome.

The presence of hiatal hernia has an important role in defective barrier function, both by removing the augmentation that the crural diaphragm provides the lower esophageal sphincter and by lowering the threshold for TLESR to occur.

Acid Clearance

The clearance of acid from the esophagus is a combination of mechanical volume clearance (gravity and peristalsis) and chemical neutralization of the lumen contents (saliva and mucosal buffering). This may be delayed in patients with reflux because of either impaired esophageal peristalsis or reduced buffering effects of swallowed saliva. The defective peristalsis can be a primary idiopathic motor disorder or, occasionally, it can result from a connective tissue disorder such as CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and

[a] Portions of this chapter were adapted from Szarka LA, DeVault KR, Murray JA. Diagnosing gastroesophageal reflux disease. Mayo Clin Proc. 2001 Jan; 76(1):97-101. Used with permission.

Abbreviations: CREST, calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; GERD, gastroesophageal reflux disease; H_2, histamine$_2$; NERD, nonerosive reflux disease; TLESR, transient lower esophageal sphincter relaxation

Box 1.1. Etiologic Factors of Gastroesophageal Reflux Disease

Motility disorders

- Transient lower esophageal relaxations[a]
- Weak lower esophageal sphincter[a]
- Weak esophageal peristalsis
- Scleroderma and CREST syndrome
- Delayed gastric emptying

Damaging factors

- Increased gastric acid production
- Bile and pancreatic juice

Resistance factors

- Reduced saliva and bicarbonate production
- Diminished mucosal blood flow
- Growth factors, protective mucus

Others

- Obesity[a]
- Hiatal hernia[a]
- Obstructive sleep apnea

Abbreviation: CREST, calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia.

[a] Major or common factor.

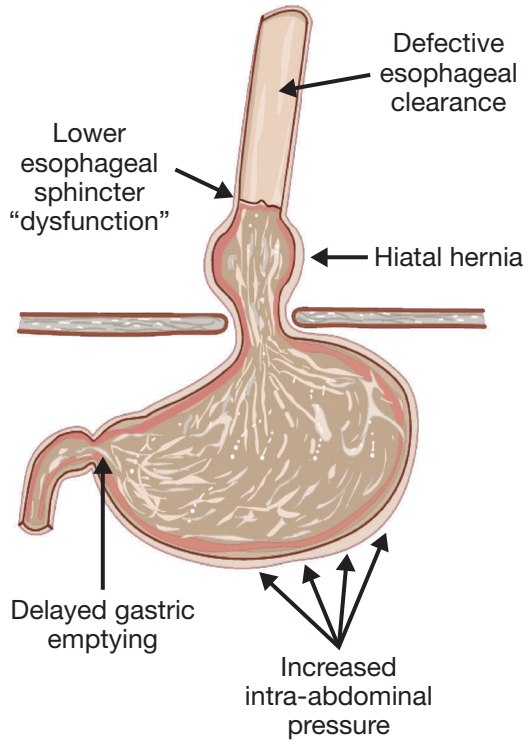

Figure 1.1. Causes of Increased Exposure of the Esophagus to Gastric Refluxate. (Adapted from AstraZeneca Pharmaceuticals LP [Internet]. Wilmington [DE]. From: http://www.astrazeneca.com. Used with permission.)

telangiectasia) syndrome or scleroderma. Many drugs and Sjögren syndrome can decrease salivary flow. Normally, salivary flow is decreased at night; thus, if reflux occurs during the night when the person is supine, acid will not be cleared by either gravity or saliva. This is why episodes of reflux at night are long-lasting and have a greater chance of causing severe injury to the mucosa.

Intrinsic Mucosal Factors

The mucosa of the esophagus has intrinsic factors that protect the esophageal lining against acid damage. These include the stratified squamous mucosa, intercellular tight junctions, growth factors, buffering blood flow, and production of mucin, bicarbonate, and epidermal growth factors. When these factors are overcome, GERD causes reflux esophagitis (Figure 1.2).

Gastric Factors

Delayed gastric emptying or increased gastric production of acid is less frequently part of GERD. Reflux esophagitis is rarely a manifestation of Zollinger-Ellison syndrome. The availability of corrosive gastric contents in the cardia of the stomach is necessary for reflux to occur during TLESR or when a defective lower esophageal sphincter is overcome during recumbency or abdominal straining. The cardia is often submerged under liquid gastric contents when a person is recumbent, especially in the right lateral decubitus position. It has been suggested that what differentiates patients with GERD from normal subjects is not the number of actual reflux events but the reflux of acidic gastric contents instead of the release of air alone. The timing of reflux is also important. Because gastric acid is buffered by food during the first hour after eating, normal physiologic reflux that may occur during maximal gastric distention is not as harmful as the reflux that occurs later after the stomach pH has again decreased. Any obstruction of the outflow from the stomach increases the propensity to reflux, although this is often associated with nausea and vomiting. Pure bile reflux may occur in patients who have had gastric surgery. More common is pathologic reflux associated with a restrictive bariatric procedure such as vertical banded gastroplasty. If too much acid-producing mucosa is present above the restriction, pathologic reflux may occur.

Obesity and GERD

It has now been established that obesity is a risk factor for GERD. An increased body mass index is also associated with Barrett esophagus and reflux esophagitis. In addition, it had already been well established that obesity is associated with an increased risk of adenocarcinoma of the distal esophagus.

Helicobacter pylori and GERD

Whether chronic *Helicobacter pylori* infection protects against GERD is a matter of controversy. Duodenal ulcers and distal gastric cancer (both caused by *H pylori* infection) are becoming rare in the developed world, and adenocarcinoma of the proximal stomach and esophagus is becoming more common as the carriage rates of *H pylori* decrease. Patients with GERD symptoms may be less likely to carry *H pylori* than the population without GERD symptoms. Reports that symptoms of GERD developed after the eradication of *H pylori* have led to a reexamination of those treatment trials of duodenal ulcers,

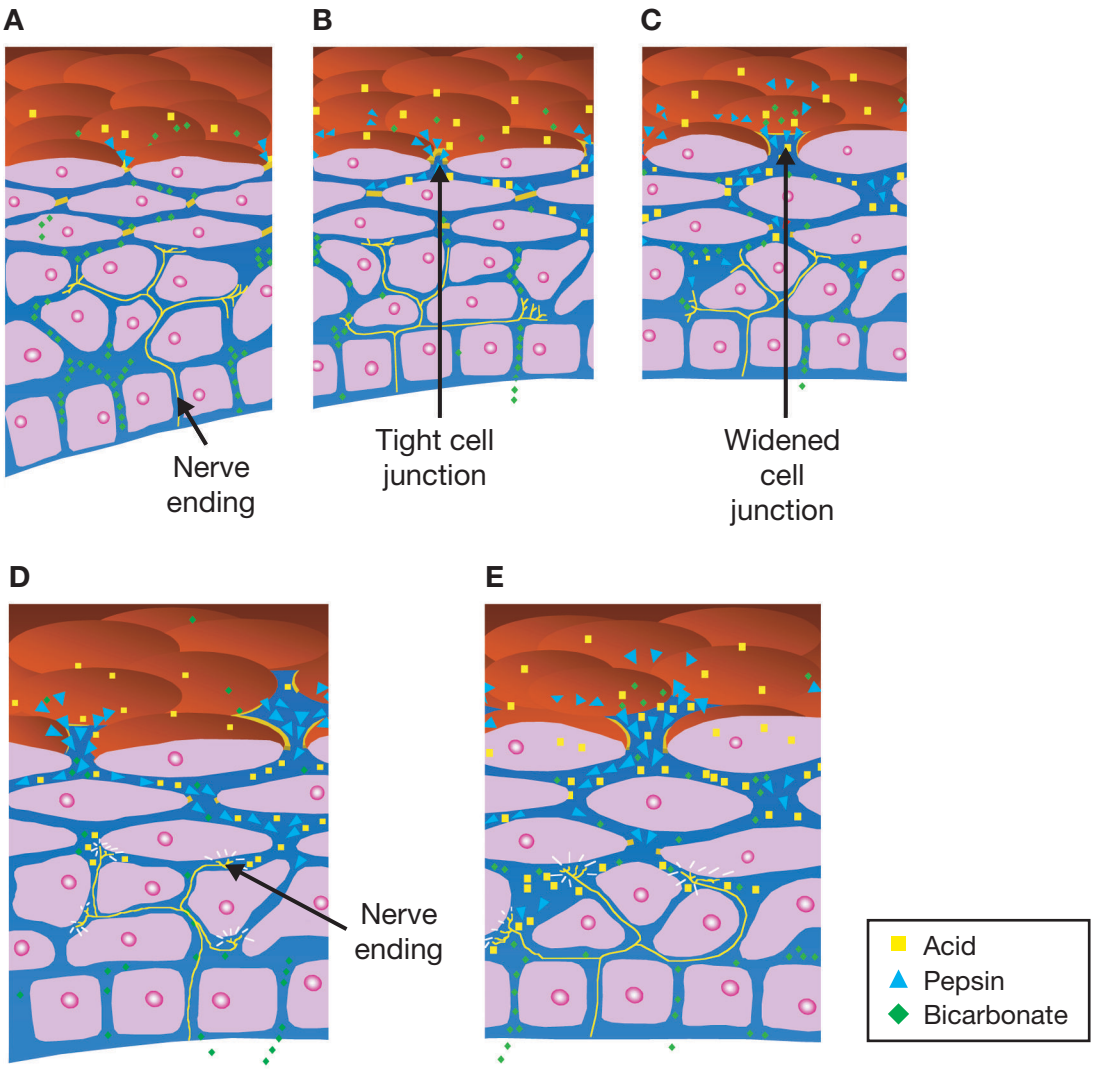

Figure 1.2. Mechanism of Action of Refluxate in Gastroesophageal Reflux Disease. The sequence of events hypothesized to lead to symptoms and tissue damage in gastroesophageal reflux disease is as follows: A and B, Acid-peptic attack weakens cell junctions. C, The cell gaps widen, thus allowing acid penetration. Exposure to gastric acid and pepsin can cause microscopic damage to the esophageal mucosa; even though the damage may not be visible endoscopically, it may still result in heartburn. D, Penetration of acid and pepsin into the mucosa allows contact of acid with epithelial nerve endings (which may result in heartburn). E, Additional influx of acid and pepsin into the mucosa triggers a cascade of events, ultimately leading to cell rupture and mucosal inflammation. (Adapted from AstraZeneca Pharmaceuticals LP [Internet]. Wilmington [DE]. From: http://www.astrazeneca.com. Used with permission.)

which included *H pylori* eradication, for the new development of GERD symptoms. The evidence is conflicting as to whether the symptoms of GERD are more common in those in whom *H pylori* eradication has been successful or in those with persistent infection. In some persons, *H pylori* infection may cause chronic atrophic gastritis that affects the corpus of the stomach, resulting in diminished acid secretion. It is this relative hypochlorhydria that protects against GERD. Indeed, it has been suggested that acid suppression heals reflux esophagitis faster in patients with *H pylori* infection (Figure 1.3).

Connective Tissue Disease

Scleroderma, CREST syndrome, or mixed connective tissue diseases are rare causes of reflux, but these should be considered in young women who have Raynaud phenomenon or subtle cutaneous features of scleroderma in the hands or face. Occasionally, GERD may be the first manifestation of these disorders. Esophageal manometry usually demonstrates a low-pressure lower esophageal sphincter and decreased amplitude of contractions in the esophagus (Figure 1.4).

Mechanism for Extraesophageal Symptoms

The mechanism for extraesophageal manifestations of GERD, such as wheeze or cough, may not always be direct aspiration or damage of mucosa in the respiratory tract but a vagally mediated reflex triggered by acidification of the distal esophageal mucosa. Subglottic stenosis and granuloma of the vocal cords are very serious consequences of reflux caused by direct contact injury of the delicate mucosa of the airway, resulting in stridor, cough, or dysphonia (Figure 1.5).

Epidemiology of GERD

GERD can be defined as chronic symptoms of heartburn, acid regurgitation or dysfunction, or injury to the esophagus or other organs because of abnormal reflux of gastric contents. Symptoms

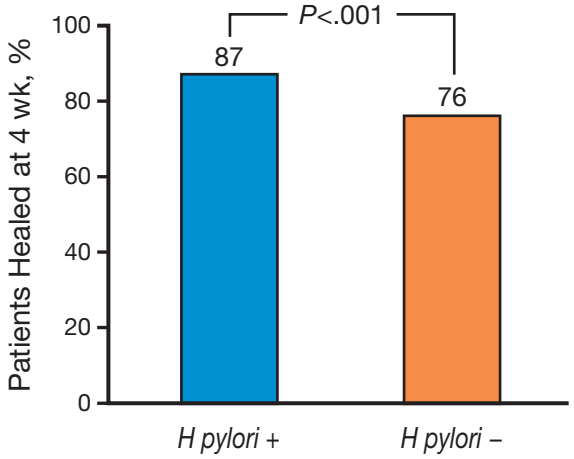

Figure 1.3. Efficacy of Proton Pump Inhibitor Therapy. The efficacy may be greater in patients with gastroesophageal reflux disease who are positive for *Helicobacter pylori* (*H pylori* +) than in those negative for *H pylori* (*H pylori* –).

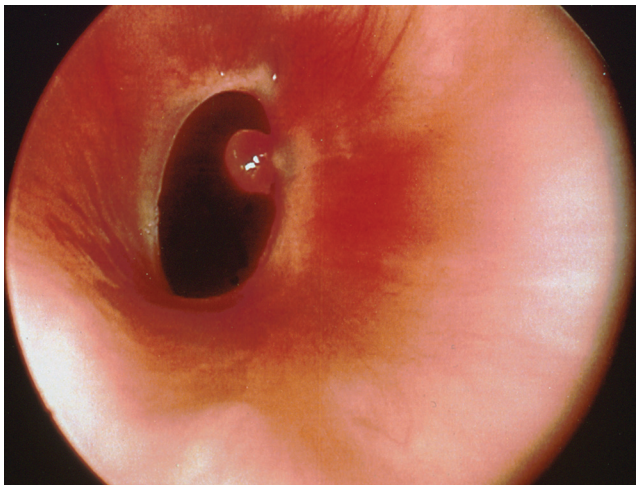

Figure 1.5. Laryngeal Stenosis. (Courtesy of Dana M. Thompson, MD, Department of Otorhinolaryngology, Mayo Clinic, Rochester, Minnesota. Used with permission.)

suggestive of GERD are common: 40% of adults in the United States report regular heartburn and regurgitation (Figure 1.6), and 18% report it weekly. GERD becomes more common with increasing age (Figure 1.7). Previously, GERD and its complications were rare in China, Japan, and other Asian countries, but this is changing rapidly with the adoption of a Western diet. A protective role of *H pylori*–induced hypochlorhydria has been suggested as a protective influence in countries with high carriage rates of infection. However, actual organ damage is observed less frequently, and less than 50% of patients who present for medical attention for reflux symptoms have esophagitis. Of patients who have endoscopy for GERD, 10% have benign strictures and only 3% to 4% have Barrett esophagus; an extremely small number have adenocarcinoma. Complications of GERD may be more common in males and whites and with advancing age. Whether reflux is becoming more common is not clear, but it certainly is diagnosed more frequently than in the past. Also, because of direct-to-consumer advertising and public education campaigns, the public is more aware of GERD.

For patients with GERD, the quality of life may be impaired even more than for those with congestive heart failure or angina pectoris (Figure 1.8). Treatment of GERD has important health economic effects because, currently, proton pump inhibitors are among the most commonly prescribed and most expensive drugs.

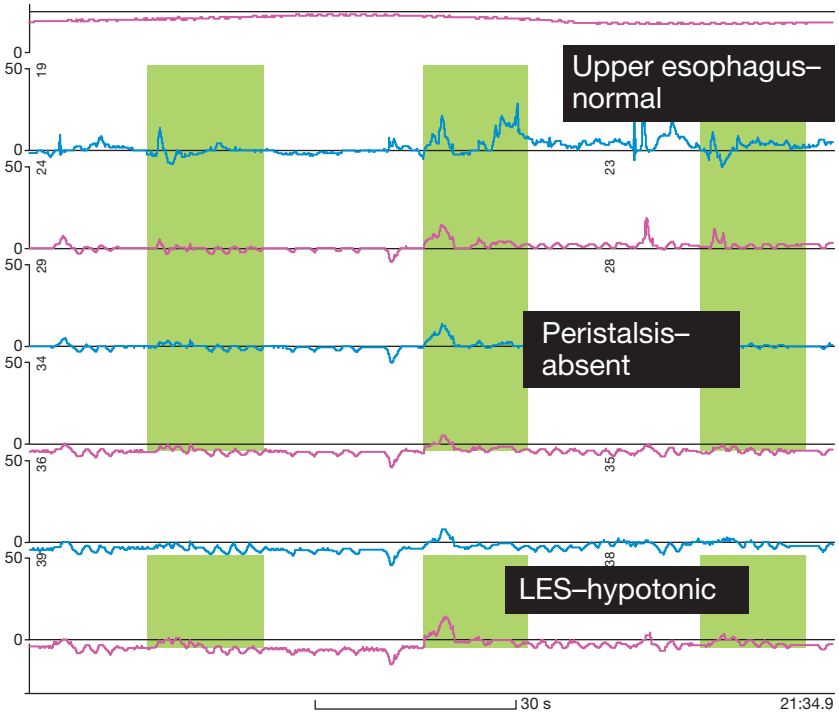

Figure 1.4. Esophageal Manometric Tracing. The tracing illustrates the complete absence of peristalsis and the hypotonicity of lower esophageal sphincter (LES) pressure consistent with esophageal involvement in scleroderma.

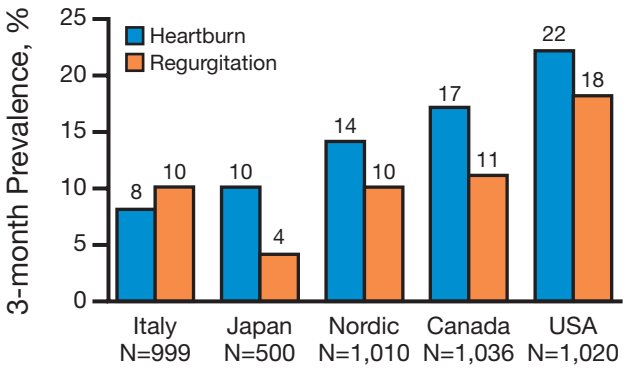

Figure 1.6. Three-Month Prevalence of Gastroesophageal Reflux Disease Worldwide. The prevalence varies markedly from country to country, largely because of differences in physicians' awareness and understanding of the condition. Nordic countries include Denmark, Finland, Norway, and Sweden. USA indicates United States of America.

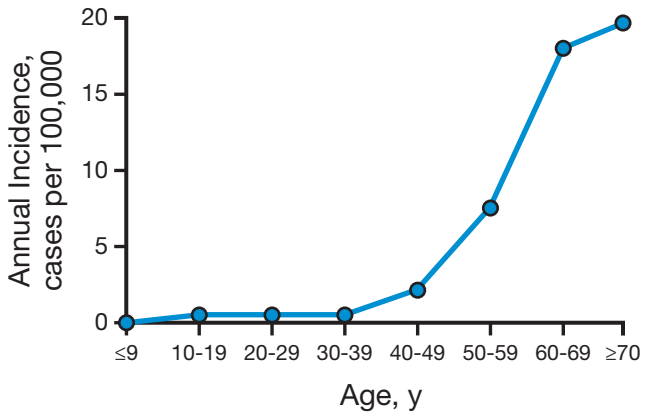

Figure 1.7. Incidence of Gastroesophageal Reflux Disease With Age. The incidence increases markedly after age 40 years. (Adapted from Brunnen PL, Karmody AM, Needham CD. Severe peptic oesophagitis. Gut. 1969 Oct;10[10]:831-7. Used with permission.)

Symptoms

The classic symptoms of GERD, that is, heartburn and acid regurgitation, are common in the general population and usually are readily recognized. GERD may be manifested in a wide array of esophageal and extraesophageal symptoms (Box 1.2). GERD may contribute to many clinical syndromes, either as a common factor or as a rare culprit.

Esophageal Symptoms

The cardinal symptoms of GERD are heartburn (defined as retrosternal burning ascending toward the neck) and acid regurgitation (the unpleasant return of sour or bitter gastric contents to the pharynx). These are to be differentiated from the nonacid (bland) regurgitation of retained esophageal contents in an obstructed esophagus, as occurs in achalasia or the almost volitional regurgitation of recently swallowed food that is remasticated and again swallowed, typifying rumination. Patient symptoms of "GERD," "reflux," and "heartburn" should be differentiated from the burning epigastric sensation of dyspepsia.

Patients may report relief of symptoms with antacids or milk. The symptoms of heartburn, and especially acid regurgitation, are specific for GERD. Their presence with sufficient frequency and severity

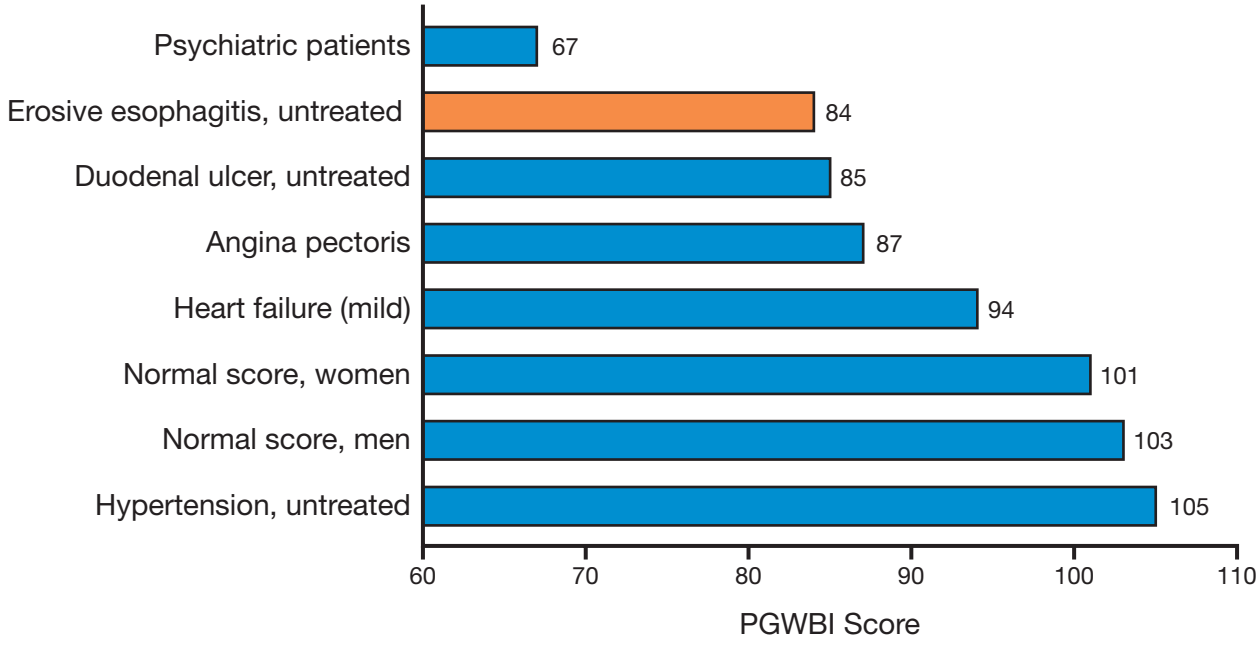

Figure 1.8. Gastroesophageal Reflux Disease (GERD) and Quality of Life. GERD has a greater effect on quality of life than other common diseases. Quality of life, assessed by the Psychological General Well-being Index (PGWBI), was compared between patients with untreated GERD and those with other disorders. For example, the mean PGWBI score for patients with untreated erosive esophagitis is similar to that for patients with untreated duodenal ulcer and lower (ie, worse) than that for patients with angina pectoris or mild heart failure. Normal scores are 101 for women and 103 for men, but they vary slightly from country to country. (Data from Dimenas E. Methodological aspects of evaluation of quality of life in upper gastrointestinal diseases. Scand J Gastroenterol Suppl. 1993;199:18-21.)

Box 1.2. Symptoms of Gastroesophageal Reflux Disease

Esophageal symptoms

- Heartburn
- Acid regurgitation
- Odynophagia
- Dysphagia
- Anginalike chest pain
- Water brash (hypersalivation)

Airway symptoms

- Cough
- Wheezing
- Hoarseness
- Throat clearing
- Globus
- Tracheal stenosis
- Aspiration pneumonia
- Pulmonary fibrosis
- Apnea in infants

alone usually justifies medical therapy. Objective confirmation is required before surgery or endoscopic treatment is recommended.

Although regurgitation of acid is a specific symptom highly suggestive of GERD, *heartburn* may have many different meanings for patients, and, indeed, patients may use different and imprecise terms to describe their symptoms, such as *indigestion, stomach upset*, and *sour stomach*. Less common symptoms suggestive of but not diagnostic of GERD include water brash (hypersalivation associated with an episode of esophageal acid exposure), dysphagia (difficulty swallowing), odynophagia (painful swallowing), and chest discomfort not identified as heartburn. Reflux is more common after eating. Although reflux symptoms can occur at any time, they tend to aggregate in the period 1 to 3 hours after eating, when acid production overcomes the buffering effects of food (Figure 1.9). It has been reported that a layer of acid may remain unbuffered on the surface of the gastric meal contents. Reflux may occur also at night or when a person with a weak lower esophageal sphincter is supine or, especially, in the right lateral decubitus position.

Esophageal Chest Pain

GERD is the most common esophageal cause of noncardiac chest pain. The pain may be referred to any point on the anterior or posterior chest, with radiation to the neck, arm, or back. It may be indistinguishable from cardiac-related pain. Because of the potentially fatal significance of cardiac-related pain, it is imperative that cardiac investigation precede esophageal investigation. Frequently, patients who have both cardiac and esophageal diseases cannot distinguish between reflux-associated pain and real angina. GERD may decrease the threshold for coronary ischemia, further confusing the clinical picture. This emphasizes the importance of first investigating the heart and, when appropriate, other vital structures.

Extraesophageal Symptoms

GERD may contribute to symptoms originating in other areas of the upper aerodigestive system. These symptoms, which can occur without the classic symptoms of heartburn and acid regurgitation, include cough, wheeze, hoarseness, sore throat, repetitive throat clearing, postnasal drip, neck or throat pain, globus, apnea, and otalgia. They are not specific for GERD. Indeed, GERD is only 1 of many causes of most of these symptoms. Like GERD, cough and wheezing are very common and likely to coexist by chance alone. Whether these symptoms are due to GERD needs to be confirmed by investigation or by the response to an empirical trial of potent acid-blocking therapy. Ideally, the demonstration of a pathologic degree of GERD and a response of the atypical symptoms to an adequate antireflux regimen are needed to conclude that GERD is the cause. GERD may produce extraesophageal symptoms in 1 of 2 ways. The first is by direct irritation or inflammation of the delicate mucosa of the larynx, trachea, or bronchi. The second is by reflex-mediated changes in function. Both mechanisms may operate in some patients.

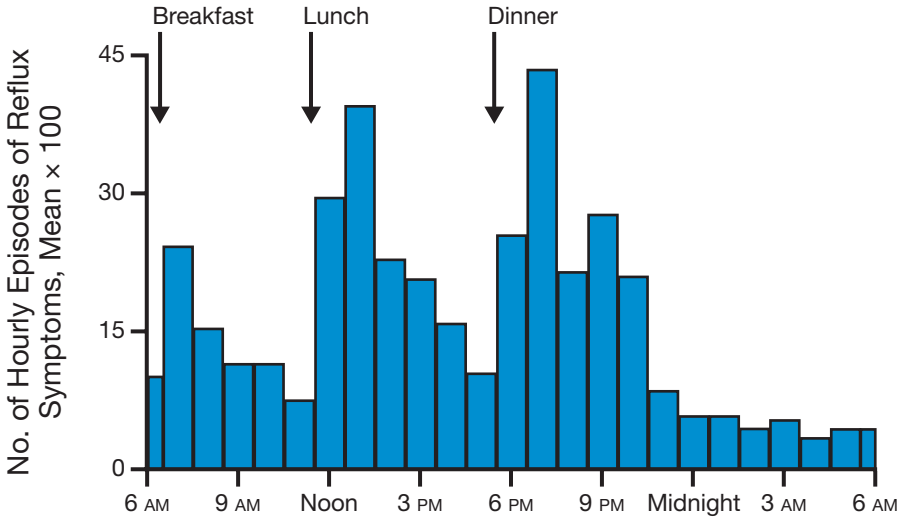

Figure 1.9. Temporal Distribution of Symptoms of Gastroesophageal Reflux Disease. Distribution of the mean number of episodes of reflux symptoms over 24 hours is shown for 105 patients who took their major meals at the same time of day. Food intake was associated with a marked increase in the number of episodes, and relatively few episodes occurred during the night. (Adapted from Johnsson L, Adlouni W, Johnsson F, Joelssson B. Timing of reflux symptoms and esophageal acid exposure. Gullet. 1992;2:58-62. Used with permission.)

Table 1.1. Empirical Trials of Acid-Suppressive Therapy With Proton Pump Inhibitors for Diagnosis

Symptom	*Treatment*	*Sensitivity,*[a] *%*	*Specificity, %*
Heartburn and regurgitation	Omeprazole twice daily for 7 d	80	56
Noncardiac chest pain	Omeprazole twice daily for 14 d	75	85
Extraesophageal	Proton pump inhibitor twice daily for 3 mo		

[a] For the confirmation of gastroesophageal reflux disease.

Establishing a Diagnosis

Therapeutic Trial

Several studies have investigated the usefulness of empirical trials of acid-suppressive therapy with proton pump inhibitors (Table 1.1).

Typical Symptoms of GERD

Patients who present with typical symptoms without alarm symptoms should be given acid-suppressive therapy. Complete resolution of the symptoms with treatment and relapse when treatment is discontinued confirm the diagnosis and suggest the need for a long-term management strategy. However, even in these patients, the specificity of a response to potent acid suppression is not specific for GERD because other acid peptic disorders respond to acid-suppressive therapy. If symptomatic improvement is limited, either an increase in dose or additional diagnostic testing is needed. If there is little or no symptomatic improvement with acid-suppressive therapy, further investigation is indicated.

Atypical Symptoms of GERD

GERD may cause or contribute to many different clinical syndromes. The more common or dangerous causes of these syndromes should be evaluated first. For example, patients with chronic cough should be evaluated for asthma, and patients with hoarseness, for laryngeal neoplasm. If GERD is a possible cause, a therapeutic trial of acid suppression may be attempted. For esophageal symptoms such as chest pain, a 2-week trial of therapy usually is sufficient. For extraesophageal symptoms, a more prolonged therapeutic trial (2-3 months) may be necessary.

The acid-suppression test uses a potent regimen of acid suppression, such as proton pump inhibitors (eg, omeprazole, 40 mg in the morning and 20 mg in the evening). If the symptoms resolve, the patient should receive long-term treatment, with an attempt at dose reduction or cessation. For atypical symptoms, it is important to consider that they may have had alternative causes that resolved spontaneously. However, if there are reversible factors that are altered and if GERD is the major cause, the symptoms are likely to recur when therapy is discontinued. If the symptoms do not resolve completely, further evaluation with upper endoscopy or 24-hour ambulatory esophageal pH monitoring with symptom-reflux correlation (or both) is indicated. Ideally, the test should be conducted when the patient is not taking a proton pump inhibitor in order to assess for acid regurgitation.

If GERD is confirmed, long-term acid-suppressive therapy is indicated. If symptoms persist, ambulatory esophageal pH monitoring may be repeated to document that the esophagus is no longer exposed to acid.

Diagnostic Tests for GERD

Diagnostic tests are unnecessary for most persons with GERD. Investigations should be conducted in patients who have alarm symptoms, equivocal results on a treatment trial, or atypical symptoms of sufficient importance to warrant confirmation of GERD and in those undergoing surgical or endoscopic therapy for GERD. For most patients, the endoscopic demonstration of esophagitis is sufficient proof of GERD and further investigation is unnecessary. However, more than 50% of patients with symptoms typical of GERD have normal endoscopic findings, with so-called nonerosive reflux disease (NERD), and additional tests are required to identify increased esophageal exposure to acid. This is typically done with ambulatory pH monitoring (Box 1.3).

Endoscopic Examination

Endoscopic examination allows direct visualization of the esophageal mucosa. In reflux esophagitis, the characteristic finding is linear erosions in the distal esophagus. These usually start at the esophagogastric junction and extend proximally for various distances. The degree of severity varies. By their appearance alone, these erosions usually are readily differentiated from rarer infectious, allergic (eosinophilic), or corrosive causes of inflammation. If the diagnosis is in question, biopsy specimens should be obtained, not primarily to confirm reflux but to identify alternative pathologic conditions.

Several grading schemes, generally based on the extent of involvement, have been used. The Los Angeles classification system is the one used most commonly worldwide (Figure 1.10). Erythema and increased vascularity are nonspecific features, and a break in the mucosa is required to make the diagnosis of reflux esophagitis. Careful scrutiny of the esophagogastric junction with adequate air insufflation is needed to examine the mucosa in its entirety. Endoscopy identifies the esophageal complications of GERD, including esophageal ulceration and stricture, Barrett esophagus, and esophageal adenocarcinoma. Alarm

Box 1.3. Uses of Diagnostic Tests for GERD

Endoscopy
- Differentiate from other causes of reflux esophagitis
- Biopsy Barrett esophagus, adenocarcinoma
- Dilate strictures
- Provide endoscopic therapy (if desired)

Contrast radiography (not recommended for GERD diagnosis)
- Identify hiatal hernia
- Identify strictures
- Reproduce reflux of barium (not sensitive)

Ambulatory 24-h pH studies
- Quantify acid reflux in the absence of esophagitis
- Determine temporal correlation between gastroesophageal reflux and atypical symptoms

Abbreviation: GERD, gastroesophageal reflux disease.

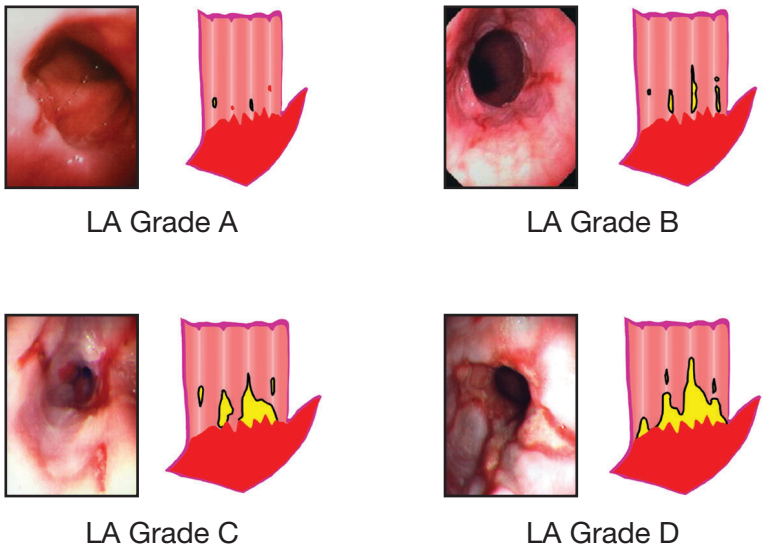

Figure 1.10. Summary of Los Angeles (LA) Classification for Erosive Esophagitis. Grade A, 1 or more mucosal breaks not more than 5 mm in maximal length. Grade B, 1 or more mucosal breaks more than 5 mm in maximal length, but not continuous between the tops of 2 mucosal folds. Grade C, mucosal breaks that are continuous between the tops of 2 or more folds but involve less than 75% of the esophageal circumference. Grade D, mucosal breaks that involve at least 75% of the esophageal circumference. (Adapted from AstraZeneca Pharmaceuticals LP [Internet]. Wilmington [DE]. From: http://www.astrazeneca.com. Used with permission.)

symptoms that suggest these complications include long duration (>10 years) of typical symptoms, dysphagia, hematemesis or melena, and weight loss. The presence of these symptoms is a strong indication for diagnostic testing, especially endoscopy. Male sex, middle age, and nocturnal heartburn may be associated with a higher risk of esophagitis and its complications.

Barium Upper Gastrointestinal Tract Series

Although the barium contrast study is a readily available test, it is of limited usefulness in the evaluation of patients with GERD and is no longer recommended for the diagnosis of GERD. Its major usefulness in GERD is in identifying strictures and large hiatal hernias. It is insensitive for detecting erosions or superficial mucosal changes. The ability to reflux barium while at rest or in response to a provocative maneuver or postural change is not a sensitive test for GERD because most patients have a normal-pressure lower esophageal sphincter. The contrast study has limited value in detecting mucosal changes other than the most pronounced inflammation, which requires a double-contrast study. The sensitivity for GERD is only 20%. When provocative maneuvers are added, the sensitivity increases but at great cost to specificity. A barium contrast study may be useful in delineating postoperative anatomical relationships and the intactness of an antireflux repair.

Prolonged Ambulatory Esophageal pH Monitoring Studies

Ambulatory pH monitoring of the esophageal lumen, a well-established test, was introduced in the early 1970s. It provides objective evidence of the degree of GERD and its timing. For most patients with symptoms of GERD and for whom the diagnosis is not in doubt, this test is not needed. The indications for ambulatory esophageal pH monitoring are listed in Box 1.4.

The test is performed with a probe that has a pH sensor at its tip. The tip is placed 5 cm above the proximal border of the lower esophageal sphincter. Accurate location of this sphincter is critical because normal values for acid exposure apply only if the distance between the pH probe and the sphincter is 5 cm. The position of the lower esophageal sphincter usually is determined manometrically with a standard esophageal manometry study or with a single pressure transducer combined with the pH probe, which can locate accurately the proximal border of the sphincter. Endoscopic measurement and pH step-up on withdrawal are not sufficiently accurate for the placement of the nasoesophageal probe. The pH is recorded by a small portable recorder. A newer method uses a tubeless pH capsule that is pinned to the distal esophagus 6 cm above the endoscopically determined squamocolumnar junction. It transmits the pH measurements to a recorder worn on the chest. Its advantages are that it can record for prolonged periods and patients may eat more normally, without the discomfort of the nasal tube. Patients should maintain their usual diet, activity, and habits during the study to allow the assessment of findings in relation to their normal lifestyle. The recorders have a patient-activated event button (or buttons) to indicate meals, changes in posture, and symptom events. The duration of the recording must be long enough to reflect all periods of the day, especially postprandial periods. Ideally, 20 hours or more of analyzable recordings are made.

Box 1.4. Indications for Ambulatory Esophageal pH Monitoring

Atypical symptoms: respiratory, ear, nose, and throat

Frequent atypical chest pain

Refractory symptoms in well-established GERD[a]

Preoperative confirmation of GERD

Abbreviation: GERD, gastroesophageal reflux disease.

[a] Done during acid blockade.

The recordings are analyzed initially by visual inspection of the graphs and then by computer-assisted quantitative analysis of the number and duration of reflux episodes and the relation to any symptoms the patient may have recorded. *Reflux of acid* is defined as a sudden decrease in intraesophageal pH to less than 4.0 that lasts longer than 5 seconds. The 6 most commonly reported measurements are the following:

1. Percentage of total time with pH <4.0
2. Percentage of upright time with pH <4.0
3. Percentage of recumbent time with pH <4.0
4. Total number of reflux events
5. Number of reflux episodes that last >5 minutes
6. Longest episode of reflux (in minutes)

The first 3 measurements of acid exposure are used most frequently in everyday practice; combined, they have a reported sensitivity of 85% and a specificity greater than 95% for diagnosing GERD associated with esophagitis. Another important strength of ambulatory esophageal pH monitoring is that it allows determination of whether a temporal relation exists between the patient's recorded symptoms and acid reflux. This determination is made initially by examining the tracing on which the symptom events have been marked and then performing a semiquantitative analysis.

Several measures have been used to calculate the correlation between symptoms and reflux, including the *symptom index* (ie, the percentage of symptom events that occur at the time of an acid reflux event). A symptom index greater than 50% usually is regarded as significant. The *symptom sensitivity index* is the percentage of reflux events associated with symptoms. A symptom sensitivity index greater than 5% usually is regarded as indicating an association between symptoms and acid reflux. More recently, the *symptom association probability* has been used as a more robust test for association. The ability to determine whether a temporal association exists depends on the number of symptom events and the amount of reflux that occurs. Patients must record their symptoms diligently and accurately during the study. If the symptoms occur once weekly, there is little use in performing pH testing.

The 24-hour ambulatory esophageal pH monitoring test has limitations. Absolute values for sensitivity and specificity have been estimated because no standards exist for comparison with prolonged ambulatory pH monitoring. Also, pH monitoring may give false-negative results in 17% of patients with proven erosive esophagitis. This may reflect day-to-day variability in reflux, or patients may have limited their diet or activities that would lead to reflux. Even simultaneous recording of pH from adjacent sensors may give different results in 20% of subjects. Some patients have a physiologic degree of acid reflux but have a strong correlation between the short-lived reflux events and symptoms. This may be due to a hypersensitive esophagus. Patients who frequently have symptoms of heartburn but no corresponding reflux may have *functional heartburn*.

Generally, pH monitoring is performed when the patient is not taking any acid-suppressive medication. However, occasionally and for specific indications, pH monitoring may be performed when a patient is taking these medications. These indications include frequent typical reflux symptoms that are refractory to what should be adequate acid-suppressive therapy with usual doses of proton pump inhibitors. Another indication is persistent extraesophageal symptoms despite high-dose proton pump inhibitor therapy in patients with confirmed reflux disease. Usually, a prerequisite for performing the test while the patient is receiving treatment is that the diagnosis of GERD is fairly certain and the intent is to verify that the suppression of acid reflux is complete.

Establishing a temporal correlation between symptoms and acid reflux events may be a secondary aim of the study. However, heartburn and regurgitation may occur in the absence of acid reflux. This may be due to nonacid reflux, gastric dyspepsia, rumination, or an unrelated process. Often, gastric pH is measured simultaneously to assess the degree of gastric acid suppression. Approximately one-third of patients receiving regular doses of proton pump inhibitors have marked production of acid in the stomach at night, but this breakthrough acid production does not always produce symptoms or actual esophageal acid reflux.

Detection of Nonacid Reflux

The main limitation of standard esophageal pH monitoring is the detection of nonacid reflux. This limitation is addressed with technology that uses a single probe to provide multilumen impedance sensor measurements and pH measurements (Figure 1.11). Indeed, this technology has become so widespread that it has largely taken over all ambulatory esophageal reflux monitoring. It is useful largely in explaining persistent or recurrent symptoms in patients who are already receiving potent acid blockade therapy. Impedance relies on the ability to identify a change in intraluminal resistance of the luminal contents. A reflux event in which there is reflux of very low impedance gastric contents into the esophagus allows for detection of this change. By arraying a series of electrodes along the catheter, it is possible to judge that this is a true reflux event by looking at the sequence.

Although this technology has been used for several years, its sensitivity for true reflux is probably about 90% with the use of computer-based algorithms for detection of reflux. It is not yet as well validated as the 24-hour pH test. The reflux events that are detected by impedance tend to be much shorter in duration than the actual change in pH; this relates to the volume of clearance of the refluxate from the esophagus. So-called volumetric clearance occurs much faster, whereas the change in pH tends to be slower because actual buffering is required. The most robust measure of abnormality of nonacid reflux is based on the frequency of the events, but there are some limitations to the system: Meals must be excluded. In patients who already have esophagitis or Barrett esophagus or retained secretions, there may be an abnormally low baseline impedance in the esophagus, which may preclude the detection of further decreases. Placement of the probe is especially crucial, since intermittent movement of the catheter into a hiatal hernia may result in spurious reflux. In addition, patients who are not receiving acid blockade therapy may have a normal number of events, but the probe may not detect the very delayed clearance at night when patients have nocturnal or supine reflux.

The major strength of this technology and its greatest utility are in looking with high fidelity at symptom-reflux correlations. The most common symptom association is regurgitation. Scoring systems have not yet evolved as they have with 24-hour pH monitoring; rather, determining the number of reflux events and the correlation with actual symptoms is the most appropriate use of this technology. It is also necessary to manually review the tracing to ensure that events identified as reflux by the monitoring system are true reflux events. Otherwise, chaotic tracings that occur after swallowing, for example, may be spuriously identified as reflux. It is especially crucial to manually review tracings where the number of events identified is close to the pathologic threshold. A threshold of 48 reflux events in patients receiving proton pump inhibitor therapy or a threshold of 73 events in patients not receiving proton pump inhibitor therapy has been suggested.

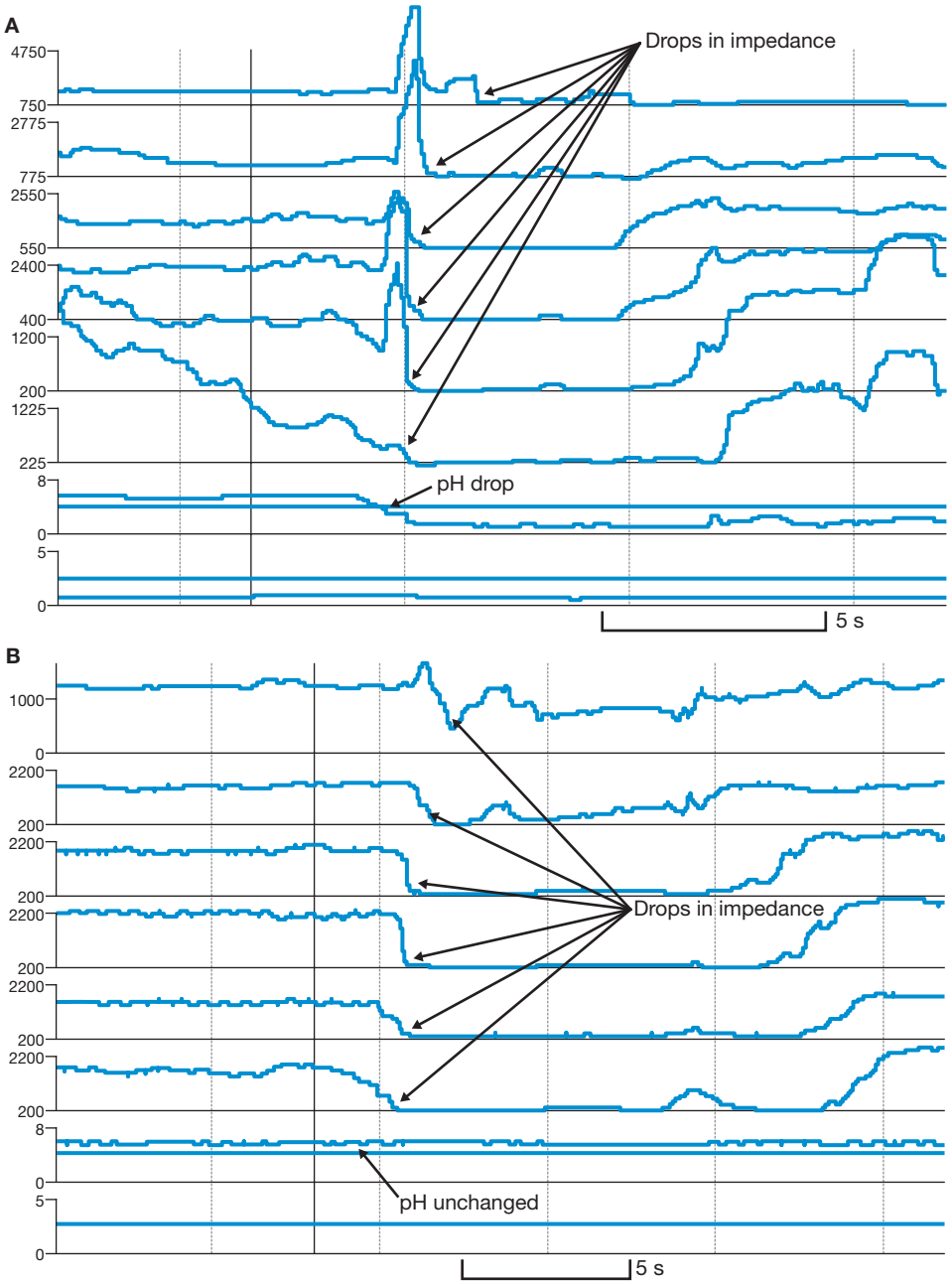

Figure 1.11. Typical Traces From Use of Multichannel Intraluminal Impedance and pH Measurements. A, Acid reflux event. B, Nonacid or weakly acidic reflux event. (Adapted from Wise JL, Murray JA. Utilising multichannel intraluminal impedance for diagnosing GERD: a review. Dis Esophagus. 2007; 20[2]:83-8. Used with permission.)

Other Tests

Gastroesophageal scintigraphy is used rarely to demonstrate gastroesophageal reflux or aspiration. The technique involves feeding the patient a technetium Tc 99m sulfur colloid–labeled meal and obtaining postprandial images with a gamma camera. Delayed images obtained the following morning may show scintigraphic activity within the lung fields, demonstrating aspiration (usually, only gross aspiration is apparent).

The Bernstein test is largely of historical interest.

Treatment

Patient- or physician-initiated empirical treatment for presumed GERD has become commonplace. Indeed, guidelines for primary care have supported this approach for patients who do not have alarm symptoms. Treatment options for GERD are summarized in Table 1.2. Potent acid suppression with proton pump inhibitors is effective and heals reflux esophagitis after only a few weeks of therapy. This has resulted in a shift in the disease as it appears to endoscopists. It is rare to find severe disease in patients who have been treated with proton pump inhibitors. This practice poses a problem when symptoms do not resolve as expected or when there is only partial improvement in symptoms. Even if the diagnosis of GERD was suggested at the time of presentation and initiation of proton pump inhibitor therapy, the disease cannot be confirmed by the usual method without stopping the medications for a substantial time, and this may not be acceptable to patients in whom proton pump inhibitors have healed the esophagitis.

Table 1.2. Summary of Treatment Options for Gastroesophageal Reflux Disease

Treatment	*Options*	*Healing Rate, %*
Lifestyle modifications	Elevate the head of the bed	20-30
	Avoid eating within 3 h before going to bed	
	Eat meals of moderate size and fat content	
	Lose excess weight	
	Reduce intake of caffeine and chocolate	
	Stop smoking	
Acid neutralization	Antacids	20-30
	Chewing gum	
	Alginate preparations	
Acid suppression	Histamine$_2$ blockers	50
	Proton pump inhibitors	≥80
Prokinetics	Metoclopramide (not useful)	30-40
Mechanical prevention of reflux	Laparoscopic surgery	≥80
	Endoscopic therapies	≥50

A careful reexamination of the pretreatment symptoms may show that what the patient thought was GERD may have been something else, for example, dyspepsia.

Acid-suppressive therapy is the cornerstone of the treatment of GERD. It provides excellent healing and relief of symptoms in patients with esophagitis or classic heartburn. The relief appears to be related directly to the degree of acid suppression achieved.

Long-term maintenance therapy is needed for most patients. Lifestyle modifications alone may produce remission in 25% of patients with symptoms, but only a few patients are compliant with the restrictions. The same principles that apply to short-term therapy apply also to long-term therapy. Less acid equals less recurrence.

Proton Pump Inhibitors

Proton pump inhibitors are absorbed rapidly and taken up and concentrated preferentially in parietal cells. They irreversibly complex with the hydrogen-potassium-ATPase pump, which is the final step in acid production. To produce acid, parietal cells must form new pumps, a process that takes many hours. Proton pump inhibitors are more potent than histamine$_2$ (H_2) blockers as suppressors of acid reflux. The healing of esophagitis and the relief of chronic symptoms are more rapid with proton pump inhibitors than with H_2 blockers. With proton pump inhibitor therapy, esophagitis heals within 4 weeks in more than 80% of patients and in virtually 100% by 8 weeks. However, the rate of complete relief from symptoms is less than the rate of healing.

Debate continues as to whether a proton pump inhibitor should be given as initial therapy and then replaced with H_2 blocker therapy or whether H_2 blocker therapy should precede proton pump inhibitor therapy. Economic analysis, which takes into account the patient's quality of life, suggests that the latter approach is preferred. It is well established that therapy sometimes can be "stepped down" successfully after treatment with a proton pump inhibitor or switched to on-demand therapy, although this is rarely suitable for patients with substantial complications of GERD.

Although routine doses of proton pump inhibitors (esomeprazole 40 mg daily, lansoprazole 30 mg daily, omeprazole 20 mg daily, pantoprazole 40 mg daily, rabeprazole 20 mg daily) are adequate for most patients with GERD, some patients may require higher or more frequent dosing to suppress GERD completely. Data have demonstrated that proton pump inhibitors are not entirely effective in blocking nocturnal production of acid in the stomach. Complete acid blockade can be achieved by increasing the dose or by adding nocturnal H_2 blocker therapy. However, nocturnal use of an H_2 blocker does not have a sustained effect, nor is it clear that complete suppression of gastric acid is desirable.

Incomplete blockade may be the result of differences in metabolism by cytochrome P450 2C19 isozyme or bioavailability. Omeprazole is absorbed more readily on an empty stomach and is most effective if the stomach parietal cells are stimulated. This is achieved by having patients eat within an hour after taking the medication.

Variable-release proton pump inhibitors that are now available can alter the pattern of release. They may be useful in patients if a stable preprandial dosing is not practical.

With maintenance proton pump inhibitor therapy, the rate of relapse of esophagitis is 20% or less, which is lower than for H_2 blockers (Figure 1.12). A slight increase in dose may be needed with long-term therapy. Also, maintenance proton pump inhibitor therapy is more effective than H_2 blockers in reducing the need for redilatation in patients with reflux-associated benign strictures.

Proton pump inhibitor therapy causes a clinically insignificant increase in the serum level of gastrin. However, no risk of carcinoid has been realized. The increase in serum levels of gastrin and parietal cell mass may lead to rebound acid secretion after the therapy is stopped. Epidemiologic studies have raised the possibility of an association between proton pump inhibitor therapy and hip fractures.

For patients who have osteoporosis and already receive proton pump inhibitor therapy, the therapy should be safe to continue. However, long-term proton pump inhibitor therapy should be used with caution in patients who have multiple other risk factors for hip fracture. Short-term use of proton pump inhibitors may be associated with an increased risk of pneumonia in the community, although long-term use is not. The effect of proton pump inhibitors, particularly omeprazole, on the metabolism of certain cardiac medications, such as clopidogrel, is not associated with increased risks of cardiovascular events. Proton pump inhibitor therapy is also a risk factor for bacterial overgrowth of the small intestine and for increased risk of *Clostridium difficile* infection.

H_2 Receptor Blockers

H_2 receptor blockers act by blocking the histamine-induced stimulation of gastric parietal cells. H_2 blockers provide moderate benefit when given in moderate doses (cimetidine 400 mg twice daily, famotidine 20 mg twice daily, nizatidine 150 mg twice daily, ranitidine 150 mg twice daily) and heal esophagitis in 50% of patients. Higher doses suppress acid more rapidly. Lower doses are less effective, and nighttime-only dosing misses all the daytime reflux that predominates. A particular role for H_2 blockers may be to augment proton pump inhibitors when given at night to block nocturnal acid breakthrough; however, tachyphylaxis prevents nocturnal H_2 blockade from producing sustained nocturnal acid suppression.

Prokinetics

The idea that a motility disorder is the genesis of GERD made a prokinetic approach intellectually enticing. Drugs such as metoclopramide and, formerly, cisapride, which increase the

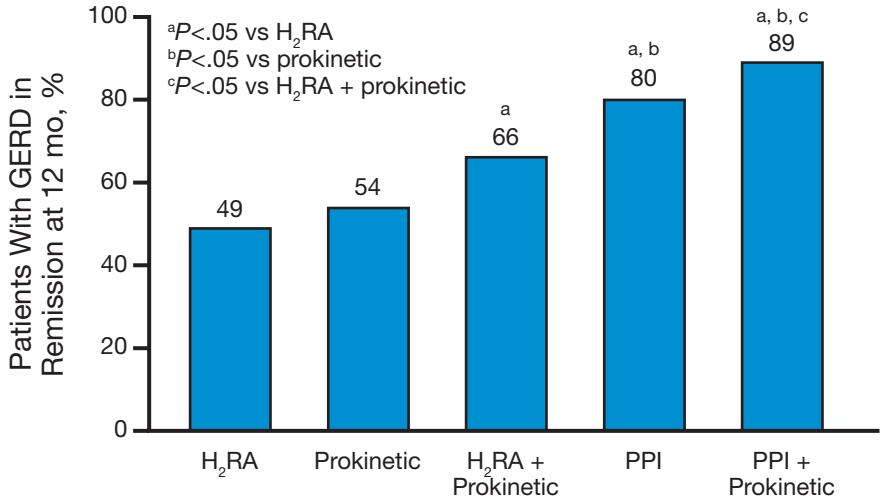

Figure 1.12. Effectiveness of Proton Pump Inhibitors (PPIs). PPIs are the most effective drugs for maintenance therapy of gastroesophageal reflux disease (GERD). Although the remission rate was slightly higher with PPI in combination with prokinetic than with PPI alone, the difference was not significant. H_2RA indicates histamine$_2$ receptor antagonist. (Data from Vigneri S, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, et al. A comparison of five maintenance therapies for reflux esophagitis. N Engl J Med. 1995 Oct;333[17]:1106-10.)

tone of the lower esophageal sphincter and esophageal clearance and accelerate gastric emptying, have been used to treat reflux. However, the healing rate and safety of these drugs have been questioned. Cisapride has been effectively withdrawn from use in the United States, and the long-term use of metoclopramide is associated with so many adverse effects that it is rarely prescribed for GERD unless that is incidental to its use for gastroparesis. Drugs that target the TLESRs also have been used, including baclofen, which probably can reduce reflux but is neither approved nor widely used for that indication.

Refractory Reflux

Refractory reflux disease can be defined as symptoms of GERD that are refractory to treatment with regular dosages of proton pump inhibitors. The many common causes of refractory reflux symptoms are listed in Box 1.5.

Functional Chest Pain

Many patients who complain the most bitterly of severe reflux often have very little reflux on 24-hour pH monitoring and have no endoscopic features of reflux. This condition has been termed *functional heartburn*. As with other functional gastrointestinal tract problems, female patients are overrepresented. Features of anxiety, panic, hyperventilation, and somatization may be clues to the diagnosis. Antacid therapies may help reduce the frequency of the symptoms, but they rarely relieve them completely. Therapies aimed at decreasing visceral hypersensitivity may be helpful (eg, a low dose of an antidepressant).

Surgical and Endoscopic Antireflux Procedures

What is the role of laparoscopic and endoscopic methods of therapy? Medical therapy has been reduced to acid neutralization or suppression of acid production. Surgeons and endoscopists have focused on the role of the mechanical or functional failure of the antireflux barrier, and this has become the prime target of various approaches for preventing the reflux of gastric contents into the esophagus.

For many years, antireflux surgery was performed through a transabdominal or transthoracic approach, with considerable morbidity. Surgical treatment was reserved for intractable reflux that the available weak medical therapy failed to cure.

With the advent of proton pump inhibitors, even severe degrees of reflux came to be well controlled, although the therapy is expensive. With the advent of minimally invasive surgery, surgical treatment has had a renaissance. The laparoscopic antireflux procedure has become a staple of the community surgeon. Its outcomes are similar to those of the open approach. With well-chosen patients and experienced surgeons, an 80% to 90% success rate is expected. The success rate decreases remarkably if the patients have symptoms refractory to proton pump inhibitor therapy or poorly documented reflux disease and if the procedure is performed by less experienced surgeons. A substantial number of these patients resume taking acid-blocking medications, often for unclear reasons.

Preoperatively, it is important to verify that the patient's symptoms are due in fact to reflux. This is accomplished by documenting reflux esophagitis and a response to proton pump inhibitor therapy or by confirming the pathologic degree of reflux with a 24-hour pH assessment while the patient is not receiving therapy. If the patient belches frequently, he or she should be informed that belching may not be possible after the operation and gas bloat may result. Preoperative esophageal manometry has been widely recommended. It identifies a severe motility disturbance such as achalasia or connective tissue disease, and some surgeons want confirmation of a weak lower esophageal sphincter (if present).

Postoperatively, 20% of patients have some dysphagia, but this persists in only 5%. Gas bloat, diarrhea, and dyspepsia may occur or become more evident postoperatively and may be troubling to patients. As many as one-third of the patients may still require proton pump inhibitor therapy postoperatively for persistent reflux or dyspepsia. Patients who have respiratory symptoms, free regurgitation, or simple but severe heartburn without gastric symptoms seem to have the best response to antireflux surgery. Female sex, lack of objective evidence of pathologic reflux, and failure to respond to proton pump inhibitor therapy all predict a poor response to surgery. Patient selection and operator experience seem to be the main determinants of a favorable surgical outcome. Reflux surgery is

Box 1.5. Causes of Refractory Reflux Symptoms in Patients Receiving Proton Pump Inhibitor Therapy

Incorrect initial diagnosis
- Nonreflux esophagitis—pill injury, skin diseases, eosinophilic esophagitis, infection
- Heart disease
- Chest wall pain
- Gastric pain

Additional diagnoses
- Dyspepsia
- Delayed gastric emptying
- Gastritis
- Peptic ulcer disease
- Nonulcer dyspepsia

Inadequate acid suppression
- Noncompliance
- Rapid metabolizers of proton pump inhibitors
- Dose timing
- Insufficient dose
- Zollinger-Ellison syndrome
- Nonacid reflux

Adenocarcinoma in Barrett esophagus
- Postoperative reflux
  - Partial gastrectomy
  - Vertical-banded gastroplasty

Esophageal dysmotility
- Spasm
- Achalasia
- Nutcracker esophagus

Functional chest pain
- Hypersensitive esophagus
- Somatic features of depression
- Functional heartburn

Free regurgitation
- Absence of lower esophageal sphincter tone
- Large hiatal hernia
- Achalasia
- Rumination

superior to long-term treatment with H_2 blockers to maintain the healing of GERD; however, follow-up for more than 10 years has shown an unexplained increase in mortality, predominantly due to cardiovascular disease, in the surgical group.

Newer surgical techniques, such as the use of a band consisting of multiple permanent magnets, have been developed and shown to have potential benefit.

Patients Who Are Not Surgical Candidates

It would be prudent to reconsider carefully the wisdom of recommending surgical therapy if a patient has symptoms that are refractory to proton pump inhibitors. A hypersensitive esophagus or gastric dysmotility may be worse after fundoplication. Also, symptoms of irritable bowel syndrome may worsen postoperatively.

Endoscopic Methods of Therapy

Several endoscopic methods have been tried or are in development for the treatment of GERD. Endoscopic methods to alter the shape or to tighten the esophagogastric junction are in various stages of development. These consist of inserting sutures or other devices into the gastric wall to generate a mechanical barrier or "speed bump" to reflux. Some endoscopic procedures are an attempt to replicate the mechanical barrier provided by fundoplication. Although some of these methods have been in clinical use, evidence for long-term efficacy is lacking.

Eosinophilic Esophagitis

The most common cause of esophagitis has been acid reflux disease; however, since the late 1990s, a truly emerging disorder, *eosinophilic esophagitis*, has come to the fore. This typically occurs in adults with dysphagia and a history of food impaction. It occurs in young adults and children and more frequently in men than in women. In children, symptoms typically are vomiting and regurgitation in addition to dysphagia. Most patients with this disorder have a history of atopy or a family history of atopy. Many have other atopic illnesses, including allergic rhinitis and asthma. Many patients have identified reactions to foods, although this is documented better in children than in adults. In addition to the classic history of episodic dysphagia or food impaction, adults who present with eosinophilic esophagitis may or may not have symptoms suggestive of reflux disease.

Diagnosis

The diagnosis can be suspected endoscopically by finding concentric rings, linear fissuring, or white plaque in the esophagus. These may occur in the proximal, middle, or distal esophagus. Occasionally, abrupt fissuring or cracking of the esophageal mucosa is reported during endoscopy. Although this can be alarming, it rarely is associated with true esophageal perforation. Rare cases have been reported of Boerhaave syndrome (ie, spontaneous esophageal rupture) or dilatation-induced perforation. Radiographic findings also can include concentric rings or so-called feline esophagus or tapered narrowing. The diagnosis is confirmed by examination of 4 or 5 biopsy samples from the esophagus. An increased number of eosinophils (>15 per high-power field) in the esophagus is required for diagnosis.

It has become apparent that *eosinophilia of the esophagus*, a more encompassing term than *eosinophilic esophagitis*, does not solely represent eosinophilic esophagitis; rather, patients with gastroesophageal reflux can also have esophageal mucosal eosinophilia that responds to vigorous acid blockade. In these patients, reflux is the primary cause of the eosinophilia and likely symptoms, and often the recommendation is to treat patients who have acid suppression and then retest them after 12 weeks of therapy.

Treatment

Treatment is largely symptomatic. The use of topical corticosteroids appears to be first-line therapy, at least for adults. In children, food avoidance strategies, including elimination diets or the "6-allergen"–reduced diet, have been used with some benefit. The use of intermittent dilatation has also been supported, particularly in adults, although many physicians would restrict the use of dilatation to dominant strictures that have resisted or have not responded to treatment with topical corticosteroids. Other agents

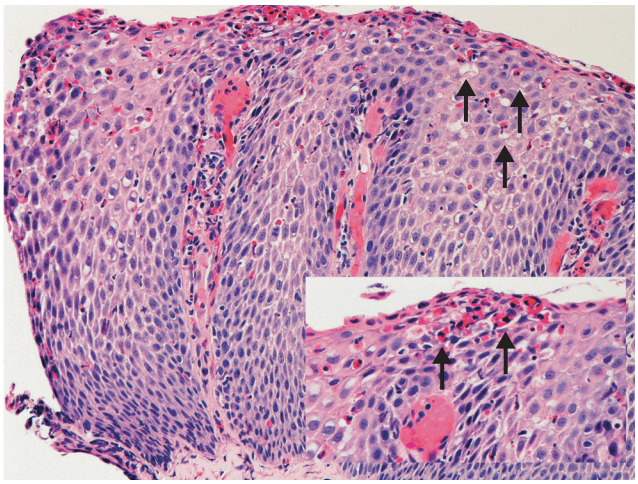

Figure 1.13. Hyperplastic Squamous Esophageal Epithelium. Many intraepithelial eosinophils are present (arrows). The superficial distribution is characteristic of eosinophilic esophagitis. Inset, A collection of eosinophils (arrows) is close to the surface. (Hematoxylin-eosin.) (Courtesy of Thomas C. Smyrk, MD, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota. Used with permission.)

have been tried, including experimental biologic therapies, to decrease the infiltration of eosinophils.

Most patients have a response to topical corticosteroid treatment and some have a response to food manipulation, but the long-term outcome is uncertain. Concerns have been raised about the possibility of scarring and stricturing that require dilatation. Occasionally, airway strictures have been described in patients with eosinophilic esophagitis.

The potential overlap between eosinophilic esophagitis and reflux esophagitis is significant. Reflux esophagitis can be associated with occasional infiltration of eosinophils in the esophagus. In contrast, eosinophilic esophagitis is associated usually with at least 15 eosinophils per high-power field. Although the appropriate threshold for making the diagnosis of eosinophilic esophagitis is debated, several eosinophils in biopsy samples, especially in samples from the middle and proximal esophagus, should strongly suggest the possibility of eosinophilic esophagitis. Sampling variation may also be a consideration because in some patients eosinophilic infiltration involves only specific locations.

It is most important to be able to recognize the typical clinical scenario: For example, a young male patient who has a history of food impaction has concentric rings or fissuring in the esophagus in a radiographic or endoscopic image. The diagnosis is made by finding a substantial number of eosinophils (>15 per high-power field) in esophageal biopsy specimens (Figure 1.13).

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2

Barrett Esophagus and Esophageal Cancer

PRASAD G. IYER, MD, MS

Barrett Esophagus

Definitions

Barrett esophagus (BE) is an acquired condition characterized by the replacement of the squamous epithelium lining the esophagus by partially intestinalized columnar epithelium. It is thought to be a complication of gastroesophageal reflux and may reflect an adaptive response to reflux of gastric contents into the esophagus. It is the strongest known risk factor for esophageal adenocarcinoma, increasing the risk by 30- to 50-fold. Endoscopic and pathologic criteria need to be met to make the diagnosis of BE. Endoscopy must demonstrate columnar-appearing mucosa in the tubular esophagus (Figure 2.1), and biopsy specimens must show intestinal metaplasia with goblet cells (specialized intestinal metaplasia) (Figure 2.2). This is based on evidence that columnar metaplasia with goblet cells in the esophagus is associated with an increased risk of progression to esophageal adenocarcinoma.

BE is characterized by proximal displacement of the squamocolumnar junction in the esophagus and has been classified into *long-segment BE* (length of visible columnar mucosa in the esophagus ≥3 cm) and *short-segment BE* (length of visible columnar mucosa in the esophagus <3 cm). *Intestinal metaplasia of the cardia* refers to the histologic finding of intestinal metaplasia with goblet cells at a normally located and normal-appearing squamocolumnar junction (Figure 2.3). This distinction is crucial because intestinal metaplasia of the cardia or the gastroesophageal junction probably is not associated with an increased risk of esophageal adenocarcinoma. Given this distinction, it is recommended that a normal-appearing and normally located squamocolumnar junction not be biopsied.

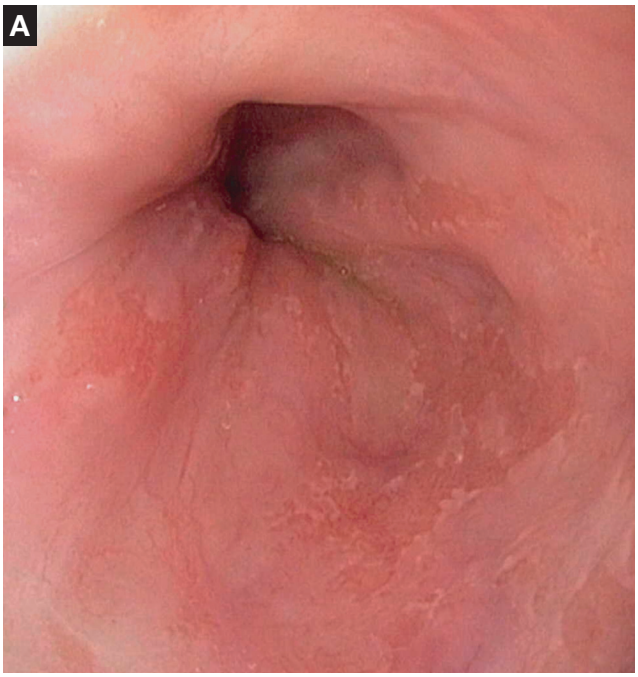
Pathophysiology

BE is thought to be a consequence of chronic reflux of gastric contents into the distal esophagus. From 5% to 15% of patients with chronic gastroesophageal reflux symptoms have evidence of BE on endoscopy. Patients with BE have longer durations of esophageal acid exposure, larger hiatal hernias, decreased lower esophageal sphincter pressures, evidence of decreased esophageal motility, and decreased esophageal sensitivity to acid reflux compared with patients without gastroesophageal reflux and those with gastroesophageal reflux but without BE. Control of acid reflux (when documented with ambulatory pH studies) in patients with BE is more difficult than in patients without BE. Resolution of acid reflux symptoms correlates poorly with control of acid reflux in patients with BE. Persistent acid reflux (documented with 24-hour pH studies) has been shown in 26% to 40% of patients with BE who are asymptomatic while receiving proton pump inhibitor therapy. Predictors of persistent acid reflux despite symptom control in patients with BE are not known.

Epidemiology

An autopsy study from Olmsted County, Minnesota, published in 1990 documented that the prevalence of long-segment BE in Olmsted County was 376 cases per 100,000 population. This study also highlighted that the prevalence of long-segment BE when assessed by autopsy was almost 20-fold the prevalence when assessed by clinically indicated endoscopy (22 cases per

Abbreviations: BE, Barrett esophagus; BMI, body mass index; CT, computed tomography; EMR, endoscopic mucosal resection; PET, positron emission tomography



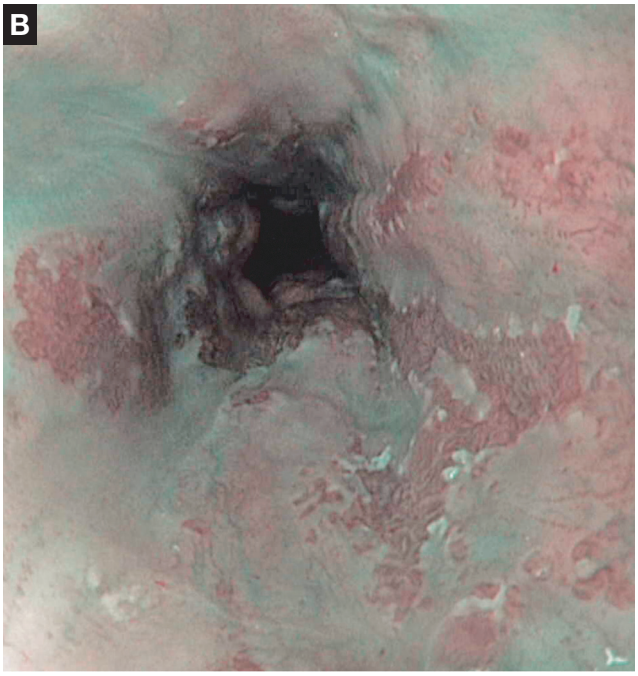


Figure 2.1. Endoscopic Appearance of Barrett Esophagus. A, Columnar mucosa in the distal esophagus on white light imaging. B, Corresponding image obtained with narrow band imaging (note tongues and islands of pink mucosa amid pale white squamous mucosa).

100,000 population), indicating that perhaps a large majority of cases of BE in the community remain undiagnosed.

Data from 2 recent population-based studies from Europe have shed additional light on the population prevalence of BE. In a Swedish study, endoscopy was performed on 1,000 participants living in 2 counties, and BE (endoscopic evidence of columnar mucosa in the esophagus with histologic confirmation of intestinal metaplasia) was reported for 16 (prevalence, 1.6%). Of note, the prevalence of BE in those with (2.3%) and without symptomatic reflux (1.8%) was not statistically different. In a second study, performed in Italy, 1,033 participants with and without reflux symptoms had endoscopy and 1.3% were found to have BE. The generalizability of these study estimates to the United States is not clear. The 2 studies may have underestimated the prevalence of BE, because of the low rate of confirmation of intestinal metaplasia in patients with endoscopically suspected BE; this may have been due to differences in the number and size of biopsy specimens taken. In addition, the threshold of the length of suspected BE for biopsy acquisition was not specified. Compared with the US population, the population studied was younger and had a higher prevalence of *Helicobacter pylori* infection (37%) and a lower prevalence of obesity (only 16% had a body mass index [BMI] >30 [calculated as weight in kilograms divided by height in meters squared]).

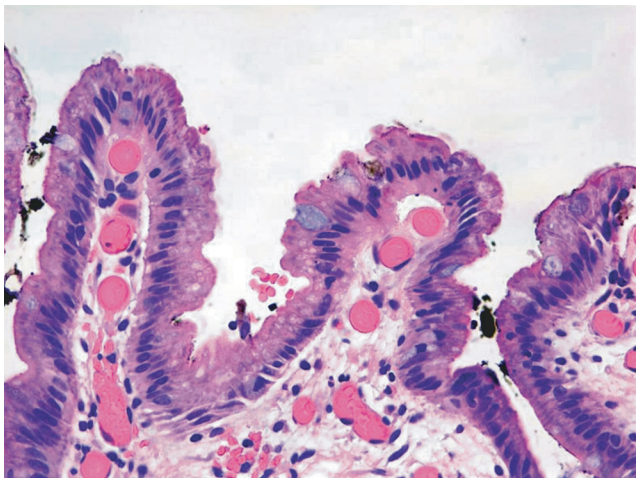


Figure 2.2. Intestinal Metaplasia With Goblet Cells. (Hematoxylin-eosin, original magnification ×400.)

Different studies have reported that the incidence of the diagnosis of BE is increasing. Whether this is due to an increasing number of endoscopic examinations is a matter of debate. A study from Olmsted County, Minnesota, showed a parallel increase in the number of endoscopic examinations being performed (Figure 2.4), whereas a study from Europe showed that the increase in the incidence of BE persisted even after adjusting for the number of endoscopic examinations.

Risk Factors

Age

BE is an acquired disorder. The prevalence of long-segment BE increases with age, particularly after the fifth decade. The mean age at the time of clinical diagnosis was 63 years in 1 population-based study. Long-segment BE is rare in children.

Male Sex

BE is more prevalent among males than females. In a Mayo Clinic study of patients who had endoscopy between 1976 and 1989, long-segment BE was twice as common in male patients as in female patients. This has been corroborated in other studies as well. In a large multicenter Italian study (patients were enrolled from 1987-1989), BE was 2.6 times more common in male patients than in female patients. In the 2005 Swedish population-based study, the male to female ratio of biopsy-proven BE was 1.5:1.

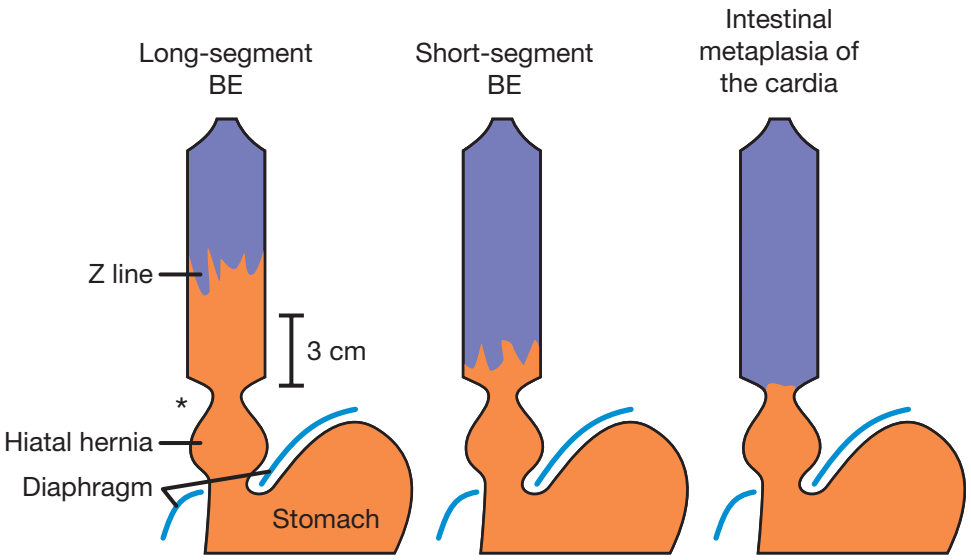


Figure 2.3. Barrett Esophagus (BE) Compared With Intestinal Metaplasia of the Cardia. Patients with long-segment or short-segment BE have columnar mucosa extending into the tubular esophagus. Biopsy specimens show intestinal metaplasia with goblet cells. If intestinal metaplasia with goblet cells is found at a normally located Z line, the patient has intestinal metaplasia of the cardia, which confers a lower cancer risk. Asterisk indicates end of tubular esophagus and beginning of stomach.

Geography and Ethnicity

BE has been described frequently in Western countries (North America, Europe, and Australia) but appears to be less common in other countries, such as Japan. However, recent reports from China, Singapore, and other Asian countries have appeared. In a recent single-center US retrospective cross-sectional cohort study of 2,100 people (37.7% white, 11.8% black, and 22.2% Hispanic) who had endoscopy from 2005 to 2006, whites (6.1%) were more likely to have BE of any length than blacks (1.6%, P=.004) or Hispanics (1.7%, P<.001).

Reflux Symptoms

BE has been described in 2% to 20% of patients with symptoms of gastroesophageal reflux (higher estimates are from referral center studies and lower estimates are from population-based studies). The duration of reflux symptoms (>5-10 years, compared with shorter durations) appears to predict the presence of BE better than the severity or frequency of symptoms. Short-segment BE is twice as prevalent as long-segment BE in patients with reflux symptoms. However, it is important to note that a substantial proportion of patients with BE (as many as 40%-50%) do not have

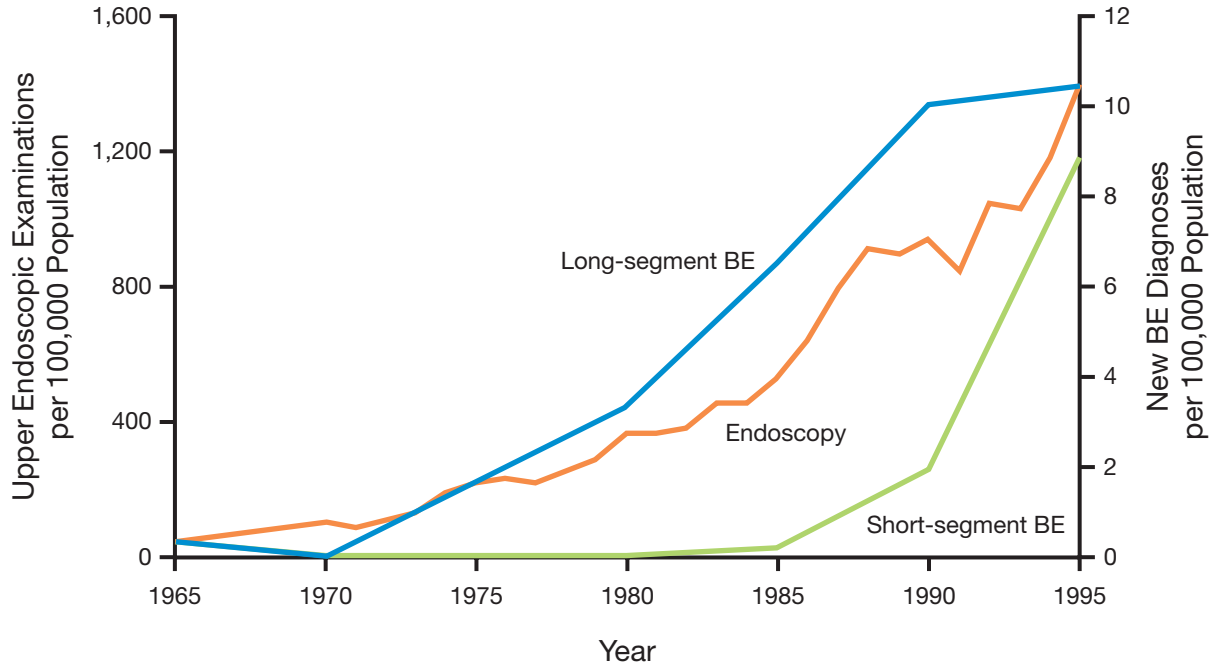


Figure 2.4. Incidence of Diagnosed Barrett Esophagus (BE) and Number of Upper Endoscopic Examinations Performed Annually in Residents of Olmsted County, Minnesota, From 1965 to 1995. (Adapted from Conio M, Cameron AJ, Romero Y, Branch CD, Schleck CD, Burgart LJ, et al. Secular trends in the epidemiology and outcome of Barrett's oesophagus in Olmsted County, Minnesota. Gut. 2001 Mar;48[3]:304-9. Used with permission.)

frequent symptoms of gastroesophageal reflux. Recent studies have reported that the association of reflux symptoms with BE is strong for long-segment BE and weak for short-segment BE.

Obesity

The association of BMI with BE has been investigated by multiple authors, but the results have been conflicting (some studies have shown an association with increased BMI and others have not). A systematic review clarified this: BMI was not significantly different between patients with BE and controls with gastroesophageal reflux disease, but it was higher in patients with BE than in normal controls. This led the authors to conclude that increased BMI may contribute to an increased risk of BE by causing increased gastroesophageal reflux, but it may not increase the risk of BE in patients with gastroesophageal reflux disease. In addition, the strong male and white predominance of BE and esophageal carcinoma is not explained by increasing obesity (as measured by BMI), which afflicts both sexes and all ethnic groups.

Visceral adiposity (in contrast to BMI as a measure of overall adiposity) may provide a better explanation for the male and white predilection of BE. The distribution of body fat is more visceral than truncal in high-risk groups (males and whites) for BE, compared with females and African Americans. Also, abdominal diameter (independent of BMI) is associated with symptoms of gastroesophageal reflux in whites but not in African Americans or Asians. Multiple groups of authors have reported an association between visceral adiposity (measured by waist circumference) and BE. A population-based case-control study found an association between increased waist circumference and the diagnosis of BE, independent of BMI (odds ratio, 2.24), when compared with population controls. This study reported a threshold of more than 80 cm of waist circumference for increased risk. The study did not find any association between BMI and BE. Another clinic-based case-control study reported that an increased waist to hip ratio, a measure of central adiposity, was associated with the diagnosis of BE (odds ratio, 2.8). The association between BMI and BE was attenuated when both waist to hip ratio and BMI were modeled together. This association is strengthened further by studies that found that abdominal obesity (measured by waist circumference) is associated with increased postprandial intragastric pressure, disruption of the gastroesophageal junction (leading to the formation of hiatal hernia), and increased transient lower esophageal sphincter relaxations in the postprandial state. A reflux-independent systemic effect of abdominal fat on esophageal inflammation and neoplasia has been postulated, mediated by proinflammatory factors, adipokines produced by visceral fat, and insulin or insulin growth factors.

Family History

Familial aggregation of BE and esophageal adenocarcinoma has been reported in multiple studies. Studies have reported the presence of confirmed BE or esophageal adenocarcinoma in first- or second-degree relatives in 7% of probands with BE or esophageal adenocarcinoma. Increased prevalence of reflux symptoms in relatives of probands with BE or esophageal adenocarcinoma has been reported, although data on increased risk of BE in relatives of probands with BE are not definitive. It is likely that BE is a complex genetic disease influenced by environmental factors. Research into identifying gene loci that may influence the risk of the development of BE is continuing.

Intestinal Metaplasia of the Cardia or Gastroesophageal Junction

The prevalence of intestinal metaplasia of the gastroesophageal junction has been reported in different studies to range from 6% to 10%. This group of patients with intestinal metaplasia appears to have different demographic characteristics from the group with BE, with a lower prevalence of reflux symptoms, no evidence of male predominance, and a higher prevalence of *H pylori* infection. Also, the prevalence of dysplasia among patients with intestinal metaplasia of the gastroesophageal junction has been reported to be lower than that among patients with BE. The natural history of intestinal metaplasia of the gastroesophageal junction is not well studied, but a small single-center study showed no progression to high-grade dysplasia or esophageal adenocarcinoma. However, because intestinal metaplasia is more common than BE, it is likely that the rate of progression to esophageal adenocarcinoma would be much lower than for patients with BE.

Cancer Risk

Among patients with BE, the rate of progression to esophageal adenocarcinoma in the absence of prevalent dysplasia was estimated to be 5 to 6 per 1,000 patient-years of follow-up. More recent European studies have reported a lower risk of progression, with a recent meta-analysis reporting a risk of progression in nondysplastic BE to be 3.3 per 1,000 patient-years of follow-up. The risk of progression in patients with low-grade dysplasia is debated, with estimates ranging from 0.6% to 1.2% per year. A recent meta-analysis reported that the rate of progression to esophageal adenocarcinoma in persons with low-grade dysplasia was 16.98 per 1,000 person-years compared with 5.98 per 1,000 person-years for persons with no dysplasia, although there was significant heterogeneity between the studies. The rate of progression among patients with high-grade dysplasia is the highest, with estimates of 65.8 per 1,000 patient-years of follow-up.

Screening

Screening for BE in patients with symptomatic gastroesophageal reflux or in the general population is a matter of controversy. Support from major gastrointestinal societies is lukewarm, with some support for screening patients with multiple risk factors. Arguments in favor of screening include the large number of cases of BE in the community that are undiagnosed and the progression of BE from gastroesophageal reflux to metaplasia, dysplasia, and adenocarcinoma (which can be detected at an early stage with a screening and surveillance program). Furthermore, retrospective studies have found that adenocarcinomas diagnosed in surveillance programs were earlier-stage adenocarcinomas and were associated with improved survival compared with adenocarcinomas diagnosed after the onset of symptoms. However, arguments against screening include the poor accuracy of symptomatic gastroesophageal reflux in predicting or excluding the absence of BE on endoscopy, the challenges with surveillance, and the lack of strong prospective evidence that screening and surveillance may improve survival of patients with esophageal adenocarcinoma. Endoscopic evaluation of patients thought to be at high risk for BE may be considered on an individual basis after discussing the pros and cons with the patient. The use of newer, less invasive methods to screen, such as unsedated transnasal endoscopy and the capsule sponge, may make screening high-risk populations more practical and cost-effective.

Surveillance

In contrast to screening, surveillance of patients with known BE is endorsed by all major gastrointestinal societies. The goal of surveillance is the early detection of progression so that therapeutic intervention may be applied to improve patient outcomes. Surveillance has a number of limitations, including the following:

1. Poor interobserver agreement between pathologists on identifying the grade of dysplasia (particularly low-grade dysplasia)
2. Variable natural predictive value of dysplasia, with variable progression rates reported for different cohorts for the same grade of dysplasia
3. The patchy distribution of advanced dysplasia, making sampling error likely during surveillance

Despite these limitations, the grade of dysplasia (no dysplasia, low-grade dysplasia, or high-grade dysplasia) is the primary clinical risk-stratification tool. Patients with long-segment BE and patients with short-segment BE both are recommended to undergo similar surveillance because the primary predictor of progression is the grade of dysplasia and there is no definitive evidence that the length of the segment of BE is an independent predictor of progression.

Before surveillance is undertaken, the pros and cons of surveillance should be discussed with the patient. Surveillance should be offered to patients with reasonable life expectancy so that therapy for progression (if detected) may be tolerated and would benefit the patient. Optimization of the acid-suppressive regimen titrated to control symptoms and to heal esophagitis should be undertaken to minimize confounding the interpretation of dysplasia grade by reactive atypia (which can occur from inflammation caused by uncontrolled reflux). Low-grade dysplasia and high-grade dysplasia should be confirmed by gastrointestinal pathologists, because there is discrepancy between community and academic pathologists in grading dysplasia and there is some evidence that the risk of progression in patients with low-grade dysplasia confirmed by expert gastrointestinal pathologists may be higher.

It is recommended that surveillance biopsies be performed after careful inspection of the segment of BE with high-resolution endoscopy to identify any visible lesions that may indicate a higher grade of dysplasia. The use of narrow band imaging or other imaging techniques that enhance superficial mucosal and vascular patterns (Figure 2.1B) may improve detection rates of focal abnormalities (such as nodules and ulcers) and advanced dysplasia. These areas should be biopsied separately and sent for histopathology study in specifically labeled bottles. The remaining BE mucosa should be biopsied in a 4-quadrant manner every 2 cm, with tissue being submitted in separate bottles at each 2-cm level. For patients with high-grade dysplasia, surveillance should be performed every 1 cm in a 4-quadrant fashion to exclude prevalent carcinoma.

No Dysplasia and Low-Grade Dysplasia

Patients with no dysplasia should be reevaluated within 12 months to exclude prevalent dysplasia and subsequently assessed every 3 to 5 years. Patients with low-grade dysplasia (Figure 2.5) should be reassessed within 6 months to exclude prevalent dysplasia, followed by annual surveillance. If no dysplasia is detected in 2 successive years, the surveillance schedule can be changed to follow the "no dysplasia" intervals. The natural history of low-grade dysplasia is somewhat variable and is characterized, in the majority of cases, by reversion to no dysplasia or stability at low-grade dysplasia.

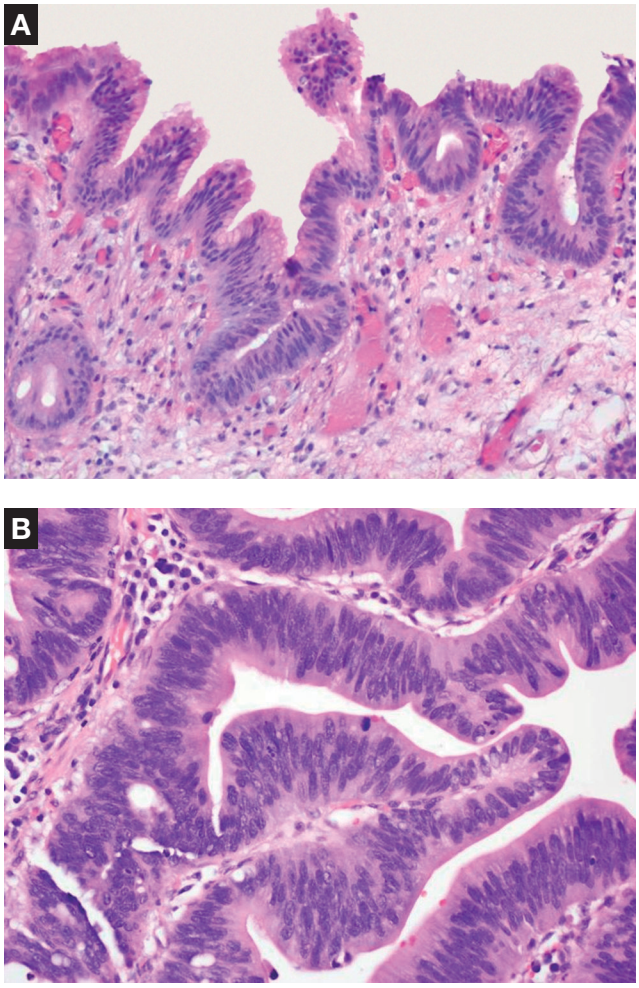


Figure 2.5. Low-Grade Dysplasia in Barrett Esophagus. A, Nuclei show evidence of stratification; they are longer, darker, and more crowded than when dysplasia is absent (Figure 2.2) (hematoxylin-eosin, original magnification ×200). B, Nuclei retain polarity toward the basement membrane and are not pleomorphic (hematoxylin-eosin, original magnification ×400). (Courtesy of Jason T. Lewis, MD, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota. Used with permission.)

High-Grade Dysplasia

If high-grade dysplasia (Figure 2.6) is detected, it should be confirmed by an expert gastrointestinal pathologist because therapeutic decisions may need to be made on the basis of the confirmation. Of note, in a multicenter randomized study for photodynamic therapy, the diagnosis of high-grade dysplasia made by a community pathologist was overruled by an expert pathologist in two-thirds of cases.

Diagnosis should be followed in 3 months by careful endoscopic evaluation, with the use of high-resolution or high-definition endoscopes (with dye-based or virtual chromoendoscopy, using techniques such as narrow band imaging), to assess for the presence of any visual abnormality. Also, endoscopic ultrasonography usually is performed to exclude the presence of a coexisting invasive neoplasm (which may be present in 10%-12% of patients treated with esophagectomy). Any visible lesion should be removed by endoscopic mucosal resection (EMR).

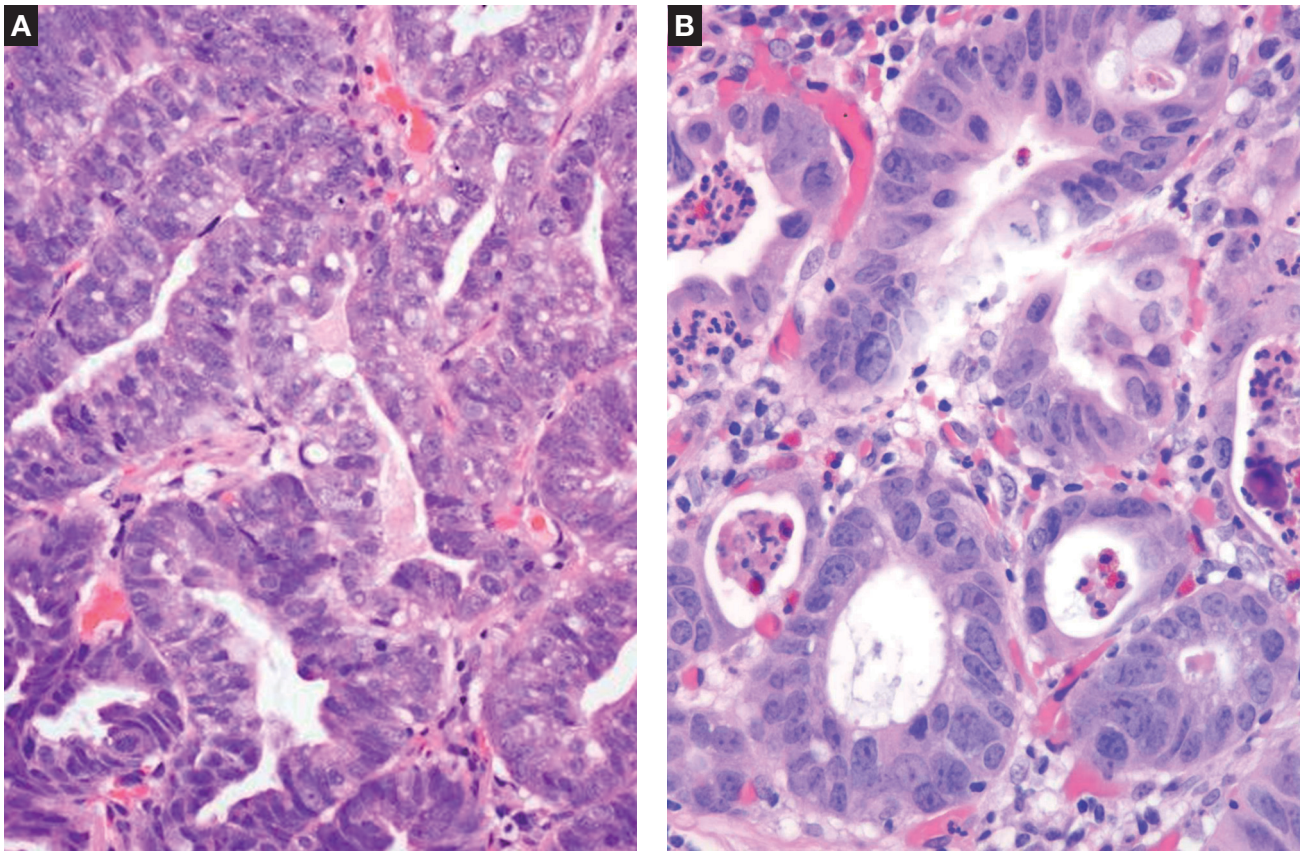


Figure 2.6. High-Grade Dysplasia in Barrett Esophagus. A, Nuclei are rounded and oriented haphazardly (not perpendicular to basement membrane), unlike in low-grade dysplasia (Figure 2.5). B, Nuclei are pleomorphic (different shapes and sizes) (hematoxylin-eosin, original magnification ×400). (Courtesy of Jason T. Lewis, MD, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota. Used with permission.)

With EMR, a submucosal injection is used to lift a mucosal lesion that is then resected by using either a plastic cap with a snare (EMR-cap) or band ligation followed by snare excision (EMR-ligation). The technique allows precise staging of the depth of invasion into the mucosa or submucosa (with better interobserver agreement between pathologists in grading dysplasia than biopsies) and the assessment of margins, and it may be therapeutic if lateral and deep margins are clear (Figure 2.7). Studies have shown that EMR of visible lesions may show that the grade of dysplasia is higher in as many as 30% of patients with high-grade dysplasia.

Options for the management of high-grade dysplasia can be divided into 3 approaches:

1. *Esophagectomy* involves removing the segment of the esophagus involved by BE and performing an esophagogastric anastomosis. It is associated with a 30-day mortality rate of 2% to 5% in high-volume centers (higher rates in lower-volume centers) and morbidity rates of 30% to 50%, including postoperative complications (eg, cardiac and pulmonary complications).
2. *Endoscopic therapy* includes additional EMR to remove any visible lesions, followed by ablation of the remaining segment of BE. Ablation is based on the concept that destruction of the metaplastic mucosa, followed by control of reflux, leads to regrowth of squamous epithelium. Several published studies have shown comparable outcomes for patients treated endoscopically or surgically. Treatment options for ablation include the following:
    a. *Photodynamic therapy* has been shown in a randomized controlled trial to be superior to surveillance in eradicating high-grade dysplasia and decreasing the risk of progression to adenocarcinoma. In a nonrandomized study, 5-year overall survival rates were comparable for patients receiving photodynamic therapy and patients undergoing esophagectomy. Photodynamic therapy makes patients intensely photosensitive and is associated with a high rate (36%) of stricture formation.
    b. *Radiofrequency ablation* involves the use of heat energy that is delivered with balloon-based catheters to destroy BE mucosa.

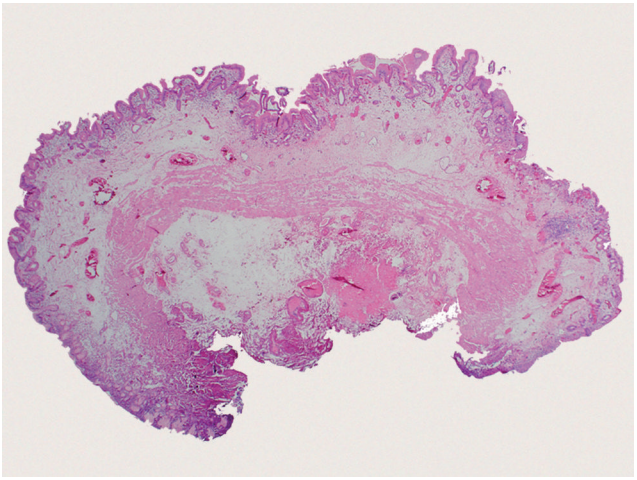


Figure 2.7. Endoscopic Mucosal Resection Specimen. This technique enables visualization of the mucosa, lamina propria, muscularis mucosa, and submucosa, thus allowing an accurate determination of the depth of invasion of malignant lesions (hematoxylin-eosin, original magnification ×12.5).

In a randomized controlled trial, radiofrequency ablation was found to be superior to sham ablation in eliminating dysplasia and metaplasia at 1 year. The technique is associated with a lower stricture rate and decreased postprocedural morbidity than with photodynamic therapy. Long-term data on durability of response are awaited. Multiple studies have reported variable rates of recurrent intestinal metaplasia following successful ablation. Other techniques such as cryotherapy, which involves the use of cryogens (liquid nitrogen and carbon dioxide) to damage the metaplastic mucosa, are being studied as alternatives, with preliminary observational reports showing efficacy comparable to that of radiofrequency ablation.

3. *Endoscopic surveillance* involves careful endoscopic evaluation every 3 months, with surveillance biopsy samples taken at every centimeter along the segment of BE, with additional endoscopic mucosal resection if a focal abnormality is visualized. This option is generally reserved for those with limited life expectancy.

The choice of treatment of high-grade dysplasia depends on whether endoscopic or surgical expertise is available at the treatment center, the choice of the patient, the fear of cancer being missed or recurring (favoring surgery) balanced with the fear of morbid surgery affecting the quality of life (favoring endoscopic therapy), the patient's ability to adhere to a long schedule of frequent endoscopic assessment in endoscopic therapy, and the overall comorbid status and life expectancy of the patient (high or low comorbid score).

Esophageal Cancer

Epidemiology

Squamous cell carcinoma (Figure 2.8A) and adenocarcinoma (Figure 2.8B) are the most common types of esophageal cancer. Esophageal carcinoma is the seventh leading cause of death in the world. Squamous cell carcinoma accounts for most cases of esophageal cancer throughout the world and is more common in Asia and the developing world; esophageal adenocarcinoma is more common in the Western world.

In the United States, approximately 16,000 cases of esophageal carcinoma are diagnosed annually, with the proportion of esophageal adenocarcinoma increasing to more than 50% since 2000. The incidence of esophageal adenocarcinoma in the United States has been increasing exponentially since the 1970s (1.0 new case per 100,000 persons per year in the 1970s to 5.69 new cases per 100,000 persons per year in 2004 for white males, and from 0.17 new cases per 100,000 persons per year in the 1970s to 0.70 new cases per 100,000 persons per year in 2004 for white females). However, the incidence of squamous cell carcinoma in the United States has decreased from 3.8 new cases per 100,000 persons per year in the 1970s to 1.90 new cases per 100,000 persons per year in 2004 for white males, with a similar trend for white females. In contrast, in certain regions of China, India, and Iran, squamous cell carcinoma is exceedingly common, occurring in 132 new cases per 100,000 persons per year.

Overall, neoplasms of the esophagus carry a poor prognosis, particularly if diagnosed after the onset of symptoms. In the United States, the number of deaths from esophageal carcinoma closely approximates the number for new cases per year, and the overall 5-year survival rate is less than 20%.

Risk Factors for Squamous Cell Carcinoma

- Geographic—The incidence rates for squamous cell carcinoma in the United States are higher in urban areas and areas with lower socioeconomic development. As mentioned above, incidence rates are higher in parts of Asia (China, India, and Iran). This may be influenced by dietary and environmental issues.
- Dietary—Known risk factors are foods with *N*-nitroso compounds (which can cause DNA damage); betel nut chewing; selenium, zinc, vitamin C, and folate deficiency; and intake of hot liquids.
- Preexisting esophageal diseases—Lye-induced strictures and achalasia are recognized risk factors.
- Other systemic diseases—Tylosis.
- Smoking and alcohol consumption—The risk of squamous cell carcinoma increases with increasing use of tobacco and alcohol.

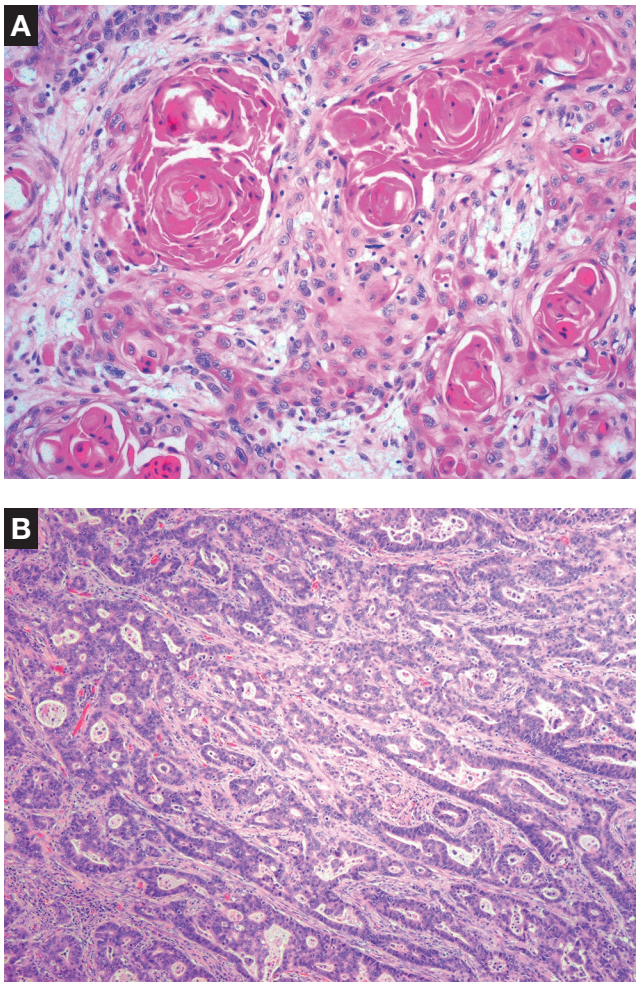


Figure 2.8. Histologic Features of Esophageal Carcinoma. A, Squamous cell carcinoma. Note irregular nests of malignant squamous cells with abnormal production of keratin (hematoxylin-eosin, original magnification ×200). B, Adenocarcinoma. Infiltrative adenocarcinoma glands with complex architecture (hematoxylin-eosin, original magnification ×100). (Courtesy of Tsung-Teh Wu, MD, PhD, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota. Used with permission.)

Risk Factors for Adenocarcinoma

The risk factors for esophageal adenocarcinoma mirror the risk factors for BE, and BE is the strongest risk factor for esophageal adenocarcinoma. Other established risk factors for esophageal adenocarcinoma are advancing age, male sex, chronic reflux of gastric contents, white ethnicity, obesity (particularly central or male pattern obesity), and smoking. Heartburn and acid

regurgitation, especially if present for more than 12 years, are also risk factors. It is important to note that as many as 40% to 50% of patients who have esophageal adenocarcinoma say that they do not have symptoms of frequent gastroesophageal reflux. Debate continues on the role of *H pylori* infection in the increasing incidence of esophageal adenocarcinoma. Some reports suggest an inverse correlation (based on atrophic gastritis from *H pylori* infection decreasing gastric acid output and, hence, decreasing reflux of gastric contents and protecting against esophageal adenocarcinoma) and other studies do not.

Signs and Symptoms

The symptoms of esophageal cancer include progressive solid food dysphagia that progresses to dysphagia to soft solids and then liquids. Unintentional weight loss is commonly reported with later-stage disease. Other than the skin changes of tylosis or lichen planus in patients with squamous cell carcinoma, there are no specific signs of esophageal cancer. In most patients, the physical examination findings are normal. With late-stage disease or disease of the proximal esophagus, supraclavicular lymphadenopathy or hepatomegaly can be palpated, indicating the possibility of metastatic disease.

Diagnosis and Staging

Diagnosis of esophageal carcinoma requires endoscopy with biopsy. Although the diagnosis may be suspected from the results of a barium study or other imaging tests, tissue to confirm a diagnosis is obtained best from endoscopy. After histologic confirmation of the diagnosis, attention should be directed at staging.

The goal of staging is to classify the tumor as early or localized to the esophagus, locally advanced, or metastatic. Tools available for staging include positron emission tomography (PET), which is best suited and most sensitive for detecting distant metastatic disease. It has greater sensitivity than computed tomography (CT), detecting unsuspected metastatic disease in 10% to 15% of cases considered negative on CT study. The use of PET has been shown to lead to a change in management in 10% to 20% of patients. However, PET is expensive and may not be widely available. CT usually is performed first to exclude metastatic disease, followed by PET (if available) to exclude any metastatic lesions missed with CT. Endoscopic ultrasonography is used to perform locoregional staging for assessing the T (tumor) stage (invasion into the esophageal wall) and the N (node) stage. Endoscopic ultrasonography is most sensitive for staging locally advanced (T2 or T3) disease, with modest accuracy for staging early (mucosal or submucosal) disease, and for establishing the N stage (particularly with the use of fine-needle aspiration of enlarged lymph nodes). Metastatic involvement of celiac lymph nodes is detected best with endoscopic ultrasonography. The current TNM staging criteria for esophageal adenocarcinoma are listed in Table 2.1.

In early-stage disease (T1N0M0), endoscopic mucosal resection is an accurate tool to distinguish between mucosally confined disease (T1a) and submucosally invasive disease (T1b). This is an important distinction because endoscopic therapy may be considered for T1a disease, given the low risk of metastatic lymphadenopathy (2%) compared with submucosal disease, for which the risk of metastatic lymphadenopathy is 20% to 30%, and the therapy of choice is esophagectomy (which allows lymph node dissection and removal) in operative candidates.

Table 2.1. TNM Staging System for Esophageal Adenocarcinoma

Stage	*Description*
Primary tumor (T)	
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, diaphragm
T4b	Unresectable tumor invading aorta, vertebral body, trachea
Regional lymph nodes (N)[a]	
N0	No regional lymph node metastasis
N1	Metastasis in 1 or 2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in ≥7 regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present

[a] The 2010 edition of the staging recommendations eliminated emphasis on the location of lymph nodes and replaced it with the number of lymph nodes involved (because the number of lymph nodes has been shown to be more prognostic of survival).

Adapted from Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A 3rd, editors; American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. New York (NY): Springer; c2010. p. 109. Used with permission.

Treatment options depend on the stage of the disease. Endoscopic therapy (with endoscopic mucosal resection and additional ablative techniques) may be considered for T1a disease; recent reports have documented excellent overall 5-year survival outcomes, in comparison with surgery. More invasive disease is treated by esophagectomy with lymph node dissection (T2 or N0 disease) or preoperative chemoradiotherapy, followed by restaging and esophagectomy (for T3 or N1 disease). This treatment strategy is based on limited data reporting a modest survival advantage with neoadjuvant chemoradiotherapy in some studies comparing neoadjuvant chemoradiotherapy followed by surgery to surgery alone. Metastatic disease can be managed with a combination of palliative chemoradiotherapy, esophageal stent placement, and nutritional support (administered orally with supplements or with percutaneously placed enteric tubes).

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3

Normal and Abnormal Esophageal Motility[a]

DAVID A. KATZKA, MD

The esophagus has 3 major functions: to facilitate passage of food and fluid boluses into the esophagus and not the airway, to propel food boluses downward to the stomach, and to keep stomach contents from refluxing upward. The esophagus accomplishes these functions by its tubular anatomy and by motility that involves the contraction and relaxation of sphincter muscles and precisely timed peristaltic waves. When these functions go awry, the most common symptoms are dysphagia and gastroesophageal reflux disease. This chapter focuses primarily on how the food bolus is handled by the esophagus.

Anatomy

The upper esophagus is shaped like a cone, in which the elastic pharynx joins the mouth to the esophagus and trachea. The upper one-third of the esophagus has a squamous cell mucosa. Its muscular layer is striated muscle. At the entry of the esophagus from the posterior pharynx is a sphincter, the *upper esophageal sphincter* (UES), consisting of the cricopharyngeus muscle (predominantly), the cervical esophagus, and the inferior pharyngeal constrictor. At rest, the UES is constricted, keeping esophageal contents from coming up into the posterior oropharynx, mouth, and airway.

The esophagus is a neuromuscular tube with an inner circular layer of muscle and an outer longitudinal layer of muscle. At the level of the aortic arch, approximately one-third the way down the esophagus, the striated muscle transitions to smooth muscle. This is known as the *transition zone*. The lower half of the esophagus consists entirely of smooth muscle. At the esophagogastric junction is a ring of thickened smooth muscle, the *lower esophageal sphincter* (LES). Like the UES, the LES is contracted at rest, keeping gastric contents from refluxing into the esophagus.

Normal Swallowing

The initial process of swallowing is under voluntary control. A swallow is initiated by the lips closing, the teeth clenching, and the tongue being elevated against the palate, forcing the bolus to the pharynx. Entry of the bolus into the pharynx triggers the involuntary swallowing reflex. This reflex involves elevation of the soft palate against the posterior pharyngeal wall to seal the oropharynx and nasopharynx and elevation of the larynx with eversion of the epiglottis over the laryngeal vestibule to prevent aspiration. The long axis of the pharynx shortens, removing the recesses formed by the piriform sinuses, valleculae, and laryngeal vestibule. Passage of the bolus stimulates peristaltic contraction of the pharyngeal muscles. As the peristaltic contraction approaches the cricopharyngeus muscle, the muscle relaxes and the larynx is elevated, actively pulling open the UES. As the contraction passes, the UES closes tightly. As the UES opens, a peristaltic wave in the esophageal body pushes the food bolus forward. The LES relaxes when the UES opens and remains relaxed until the bolus has entered the stomach.

[a] Portions of this chapter were adapted from Ferguson DD, DeVault KR. Dysphagia. Curr Treat Options Gastroenterol. 2004 Aug;7(4):251-8 and Francis DL, Katzka DA. Achalasia: update on the disease and its treatment. Gastroenterology. 2010 Aug;139(2):369-74. Epub 2010 Jun 18. Used with permission.

Abbreviations: CREST, calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; EGD, esophagogastroduodenoscopy; LES, lower esophageal sphincter; UES, upper esophageal sphincter

Relaxation of the LES occurs through the release of nitric oxide from myenteric neurons that innervate the LES. Myenteric neurons are important also in maintaining the resting basal tone of the upper esophagus. Peristaltic contractions are under local control of the myenteric plexus. In this process, acetylcholine has an excitatory effect and nitric oxide has an inhibitory effect.

The smooth muscle of the esophagus is innervated by axons of cranial nerve X (vagus nerve) that originate in the dorsal motor nucleus of the vagus and synapse on myenteric plexus neurons in the esophagus. The striated muscle of the pharynx, the UES, and the striated muscle in the proximal esophagus are innervated by cranial nerves IX (glossopharyngeal nerve) and X.

Swallowing Dysfunction

Oropharyngeal Swallowing Disorders

Oropharyngeal dysphagia is often characterized by the complaint of difficulty initiating a swallow, transitioning the food bolus or liquid into the esophagus, meal-induced coughing or "choking," or of food "getting stuck" in the voluntary phase of swallowing. Notably, liquids are frequently more difficult to swallow than solids. The patient often localizes the sensation to the cervical esophagus above the suprasternal notch.

Many disorders cause oropharyngeal dysphagia (Table 3.1). Generally, these include neuromuscular diseases, systemic diseases, and mechanical obstruction. When neuromuscular diseases cause oropharyngeal dysphagia, other neurologic or muscular symptoms may be present given that the cranial nerves and central mechanisms that control the oropharyngeal phase of swallowing also control the muscles necessary for other functions, such as speaking (tongue motion), oral bolus retention, and laryngeal protection. As a result, common symptoms in oropharyngeal swallowing disorders include recurrent bouts of aspiration pneumonia from inadequate airway protection, hoarseness, dysarthria, and pharyngonasal regurgitation. Oropharyngeal dysphagia can be caused also by mechanical or anatomical abnormalities, such as cervical osteophytes, thyromegaly, pharyngeal tonsillar enlargement, a cricopharyngeal bar (also known as hypertensive UES), and squamous cell carcinoma.

Table 3.1. Causes and Treatment of Oropharyngeal Dysphagia

Cause	*Treatment*
Neuromuscular disorders	
Amyotrophic lateral sclerosis	Swallowing rehabilitation therapy
Brainstem tumors	
Cerebrovascular accident	
Head injury	
Peripheral neuropathy	
Phenothiazines	
Muscular dystrophies	
Poliomyelitis	
Multiple sclerosis	Swallowing rehabilitation therapy Medical treatment of underlying disorder
Parkinson disease	
Myasthenia gravis	
Polymyositis, dermatomyositis	
Mechanical obstruction	
Cricopharyngeal bar	Bougie dilatation, botulinum toxin injection, cricopharyngeal myotomy with diverticulectomy
Zenker diverticulum	
Thyromegaly	Medical treatment Surgery in severe cases
Cervical osteophyte	

A Zenker diverticulum causes dysphagia through a combination of dysmotility and mechanical obstruction. With aging, the cricopharyngeus muscle becomes fibrotic, leading to poor compliance, which can lead to some degree of dysphagia. As a result, increased pressure in this area leads to diverticulum formation in the Killian triangle, an area of relative pharyngeal weakness between the inferior pharyngeal constrictor muscle and the cricopharyngeus muscle. As the diverticulum enlarges, it causes food trapping as well as extrinsic compression and narrowing on the esophagus distally.

The best way to evaluate oropharyngeal dysphagia is with a videofluoroscopic swallowing study in the presence of a speech and swallowing therapist. This test allows thorough evaluation of the first portion of a swallow. It also can be used to determine whether the problem is functional or anatomical and to target treatment. Specifically, the following functions are evaluated:

- Tongue coordination—An uncoordinated tongue impairs transmission of the bolus.
- Soft palate elevation—Dysfunction of the soft palate can lead to nasopharyngeal regurgitation.
- Laryngeal closure—Failure of laryngeal closure can lead to aspiration.
- Pharyngeal peristalsis—Poor pharyngeal peristalsis results in residue in the valleculae or piriform sinuses, requiring multiple swallows and often leading to aspiration.

The primary treatment of oropharyngeal dysphagia is swallowing rehabilitation by a swallowing professional (in most cases, a speech pathologist). Swallowing rehabilitation benefits most patients who have oropharyngeal dysphagia. In addition to swallowing rehabilitation, any patient with oropharyngeal dysphagia should be cautioned to chew food thoroughly and slowly and to avoid drinking alcohol during meals. Consuming food quickly and without focused attention can easily lead to aspiration, the most important risk of oropharyngeal dysphagia. Smoking also increases the risk of aspiration.

A number of exercises and maneuvers performed during swallowing may reduce oropharyngeal dysphagia and can be tailored to target a specific defect. Some authors think that swallowing rehabilitation can improve oropharyngeal dysphagia even when it is caused by an anatomical abnormality. This has been demonstrated in patients with defects due to surgical resection of oropharyngeal tissue or caustic injury.

Patients who have oropharyngeal dysphagia due to an anatomical abnormality, such as a Zenker diverticulum or a cricopharyngeal bar, typically require endoscopic or surgical intervention. Bougie dilation has been used successfully in some patients with oropharyngeal dysphagia caused by a cricopharyngeal bar, hypertensive UES, or primary cricopharyngeal dysfunction. Injection of botulinum toxin at the UES also has been effective for hypertensive UES or a Zenker diverticulum.

Patients with inadequate pharyngeal contraction or lack of coordination between the hypopharynx and the UES, a cricopharyngeal bar, hypertensive UES, or a Zenker diverticulum may be candidates for cricopharyngeal myotomy. The success of myotomy depends on the patient having adequate neuromuscular function and either radiographic evidence of obstruction to bolus flow at the level of the cricopharyngeus muscle or manometric evidence that the UES pressure is greater than that of the pharynx.

Pharmacologic intervention is available for patients with oropharyngeal dysphagia caused by an underlying neurologic disease that has effective medical therapy, such as myasthenia gravis or Parkinson disease. As a result, it is important to consider referral to a neurologist, otorhinolaryngologist, or rheumatologist.

Preliminary evaluation with blood tests (creatine kinase and antinuclear antibody) and imaging (magnetic resonance imaging of the brain) may be considered. Many patients with oropharyngeal dysphagia have an underlying disease that is progressive and does not have any effective treatment option. For these patients, swallowing rehabilitation may prolong the time they can meet their nutritional needs orally, but ultimately many require nonoral feeding to prevent aspiration (eg, with a percutaneous gastrostomy tube).

Esophageal Body Disorders

Patients with an esophageal body or LES disorder describe esophageal dysphagia characterized by the onset of symptoms moments after the initiation of a swallow. They usually can sense that the food or liquid bolus has traversed the oral cavity and has entered the esophagus. They complain of food feeling "stuck" or "hung up" in transition to the stomach. They may feel symptoms in the retrosternal area or near the suprasternal notch. Retrosternal dysphagia usually corresponds to the location of the lesion, whereas suprasternal dysphagia is referred from below as much as 80% of the time. Occasionally, esophageal dysphagia can be so profound that patients describe dysphagia in addition to regurgitation during, or just after, a meal.

Esophageal dysphagia can be caused by several diseases but is most often the result of a mechanical obstruction or 1 of a small number of motility disorders. Esophageal dysphagia caused by a motility disorder is commonly characterized by dysphagia with both solids and liquids. Dysphagia associated with only solid foods is more likely due to a mechanical obstruction, although a mechanical obstruction may progress to the extent that dysphagia is associated with both solids and liquids.

Episodic and nonprogressive dysphagia without weight loss usually is due to an esophageal web or distal esophageal ring. If solid food dysphagia is progressive, the problem may be an esophageal stricture, carcinoma of the esophagus, or achalasia. When weight loss is present with solid food dysphagia, the most important concern is esophageal carcinoma.

Esophageal dysphagia is an alarm symptom and merits investigation of the cause. A small number of tests are available to evaluate esophageal dysphagia: upper gastrointestinal endoscopy, barium esophagography, and esophageal manometry. The goal of testing is to identify structural or mucosal abnormalities that require intervention, to detect underlying systemic disease, and to define functional disorders.

The choice of an initial test is based on the clinical presentation and the expertise available. Typically, a barium esophagram or upper gastrointestinal endoscopy is the first test. Barium esophagram can be helpful if a motility disorder is suspected or to plan endoscopic therapy, if appropriate. For example, if a Schatzki ring is identified, a plan can be made for endoscopy with dilation. Many experts recommend that if patients with esophageal dysphagia have no endoscopic evidence of mechanical obstruction, esophageal biopsy specimens should be obtained to rule out eosinophilic esophagitis. If testing for eosinophilic esophagitis is negative, most experts recommend proceeding with barium esophagography or high-resolution esophageal manometry with impedance measurement (or both) (Figure 3.1).

Esophageal Motility Disorders

Disorders of esophageal motility are diagnosed with high-resolution esophageal manometry. Examples of normal manometric recordings of primary peristalsis are shown in Figure 3.2. With a liquid bolus, the esophageal body peristaltic wave moves at a rate of 2 to 8 cm/s, followed by complete relaxation of the LES. The LES is tonically closed at rest, with a normal mean pressure between 10 and 45 mm Hg. At relaxation, the normal residual pressure of the LES is less than 8 mm Hg. The normal average amplitude of the distal wave is 30 to 220 mm Hg.

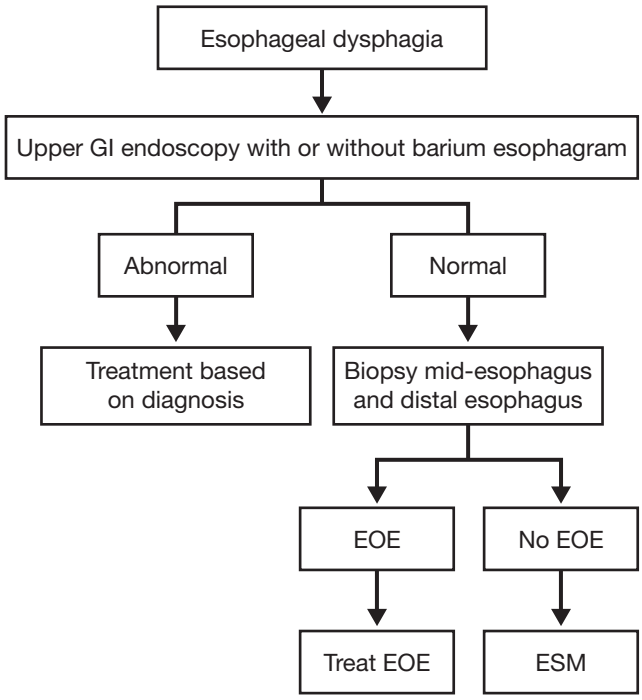

Figure 3.1. Algorithm for Diagnostic Evaluation of Dysphagia. With endoscopy, barium esophagram is optional; some authors recommend an initial barium esophagram to guide endoscopic intervention. EOE indicates eosinophilic esophagitis; ESM, esophageal manometry; GI, gastrointestinal.

Classification of Esophageal Motility Disorders

Esophageal motility disorders generally are classified into achalasia and related disorders (eg, diffuse esophageal spasm), nonspecific disorders (eg, nutcracker esophagus), and a series of nonspecific manometric abnormalities (eg, hypotensive or failed peristalsis, LES hypotension or hypertension with or without relaxation). Diffuse smooth muscle myopathies may also be well characterized by manometric analysis. An additional test, impedance measurement, is now standard on most manometry catheters. Impedance allows for measurement of bolus transit and clearance in the esophagus simultaneously with manometric pressure measurement. All these esophageal motility disorders have diagnostic criteria (Table 3.2). Most recently, the Chicago Classification has been developed, and it has been adapted by many physicians as an emerging method of classifying esophageal dysmotility disorders.

Achalasia

Of all esophageal motility disorders, achalasia is the most important to diagnose and treat because failure to do so can result in significant patient morbidity. Achalasia is the loss of peristalsis of the esophageal body and failure of relaxation of the LES.

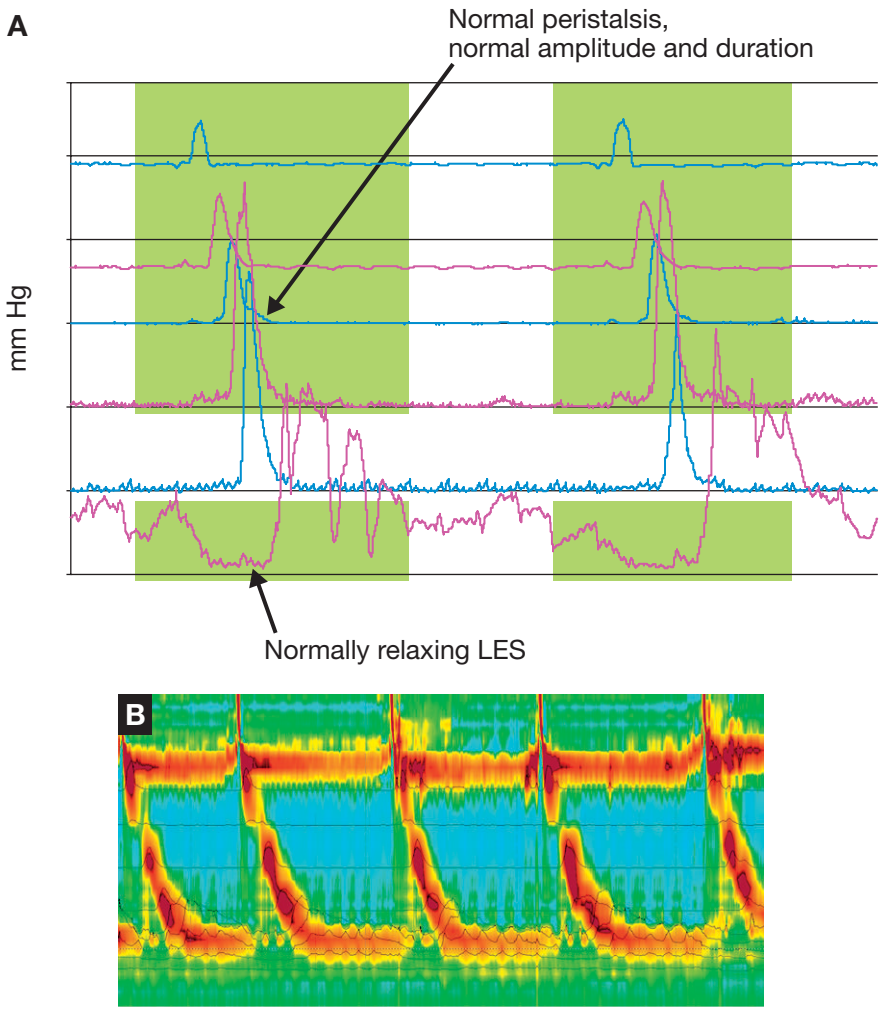

Figure 3.2. Normal Peristalsis on Esophageal Manometry. A, Esophageal manometry showing normal peristalsis (with normal amplitude and duration) and a normally relaxing lower esophageal sphincter (LES). B, High-resolution manometry Clouse plot from a patient with normal peristalsis and upper esophageal sphincter and LES function.

Achalasia is rare, with most studies reporting an incidence of 1 per 100,000 persons and a prevalence of 10 per 100,000 persons. There is no sex or race predominance, and the disease can occur at any age. A diagnosis of achalasia before the second decade of a patient's life is rare. The incidence increases with age, with the highest incidence in the seventh decade.

Achalasia is best described as primary or secondary. Primary and secondary achalasia share many of the same clinical features, but while primary achalasia occurs without an associated event or condition, secondary achalasia has a cause that can be identified. The most common cause of secondary achalasia worldwide is an infection by *Trypanosoma cruzi* (a species found in Central and South America) known as *Chagas disease*. This infection also affects other organs and can cause megacolon, heart disease, and neurologic disorders.

Other causes of secondary achalasia are infiltration or obstruction of the LES by systemic disease or direct invasion by tumor, amyloid, peripheral neuropathy, or central nervous system disorders. Secondary achalasia can be iatrogenic, most commonly from an incorrectly constructed fundoplication during antireflux procedures. Secondary achalasia has been reported also with laparoscopic adjustable gastric banding.

Pathology

The most striking pathologic characteristic of achalasia is the degeneration of ganglion cells in the myenteric plexus of the esophageal body and LES. Immunohistochemical techniques show that the loss of ganglion cells is in association with lymphocytic infiltration, which has led to the proposition that the cause of the condition is an autoimmune response or an immune response to a viral infection.

The cause of ganglion cell degeneration in achalasia has been investigated, but a clear etiology has not been defined. An inflammatory reaction induced by viral infection has been studied with measles, herpesvirus, varicella-zoster virus, poliovirus, and human papillomavirus, with inconsistent results among studies. The role of an autoimmune process has been studied as a potential cause. Most investigators have focused on the association of specific HLA classes with achalasia. Potential associations have been shown with the class II antigen HLA-DQw1. There is evidence of myenteric antiplexus antibodies with specific HLA genotypes. Of note, a recent case-control study examined the serum from 70 patients with primary achalasia and found a higher prevalence of neural autoantibodies in patients than in controls. Because the study of the role of autoimmunity in gastrointestinal

Table 3.2. Diagnostic Criteria, Common Symptoms, and Treatment Options for Esophageal Motility Disorders

Esophageal Motility Disorder	*Manometric Diagnostic Criteria*	*Symptoms*	*Treatment Options*
Achalasia	Absence of distal peristalsis Incomplete LES relaxation (residual pressure >8 mm Hg) Increased resting LES pressure (≥45 mm Hg)[a]	Dysphagia, chest pain, regurgitation, weight loss, nocturnal cough, aspiration pneumonia	Medications[b] Botulinum toxin Rigid balloon dilation Esophagomyotomy
Nonspecific esophageal dysmotility			
Discoordinated motility			
Diffuse esophageal spasm	Simultaneous contractions (≥20% wet swallows) Intermittent peristalsis Repetitive contractions (≥3 peaks) Prolonged duration of contractions (>6 s)	Chest pain, dysphagia	Medications Botulinum toxin For severe cases, long esophagomyotomy
Hypercontractile esophagus			
Nutcracker esophagus	Increased distal peristaltic amplitude (mean ≥220 mm Hg) Increased peristaltic duration (mean >6 s)	Chest pain, dysphagia	Medications Bougie dilation Botulinum toxin
Hypertensive LES	Resting LES pressure >45 mm Hg With or without incomplete relaxation (residual pressure >8 mm Hg)	Chest pain, dysphagia	Medications Botulinum toxin
Hypocontractile esophagus			
Ineffective esophageal motility	Low-amplitude peristalsis (>50% wet swallows) Low mean distal peristaltic amplitude (<30 mm Hg)	Reflux, regurgitation, dysphagia	Treat underlying disorder Acid-suppressing medications Fundoplication (typically partial)
Hypotensive LES	Resting LES pressure <10 mm Hg	Reflux, regurgitation	Acid-suppressing medications Fundoplication (typically partial)

Abbreviation: LES, lower esophageal sphincter.
[a] Increased resting pressure is not required for diagnosis of achalasia; as many as 50% of patients have normal resting pressure. Absence of peristalsis and poorly relaxing LES are required for diagnosis.
[b] Medications are typically ineffective and poorly tolerated in achalasia. Most authors do not recommend medical treatment of achalasia.

motility disease is recent, it is possible that an autoantibody that causes primary achalasia has yet to be discovered.

Diagnosis

Classic symptoms of achalasia include dysphagia to liquids and solids, regurgitation, chest pain, and weight loss. Most patients do not have all these symptoms, however. Patients who have a symptom complex that suggests achalasia typically require at least 2, and sometimes 3, studies for diagnosis. A barium esophagram is often the first study performed. In achalasia, this study classically shows a dilated esophagus, absence of peristalsis, and narrowing of the distal esophagus in a typical bird's beak appearance (Figure 3.3).

Endoscopic evaluation of the esophagus and stomach is recommended for every patient with achalasia to ensure that radiographic or manometric findings are due to achalasia rather than to an obstructive disorder that can have a similar manometric or radiographic appearance, most importantly, a tumor of the distal esophagus. Normal esophagogastroduodenoscopic (EGD) results should not dissuade a clinician from making the diagnosis of achalasia, because up to 40% of patients with this disease have normal findings on endoscopy.

Esophageal manometry is considered the "gold standard" test for achalasia. Classic achalasia is defined by the absence of peristalsis in the esophageal body, a hypertensive LES (resting pressure >45 mm Hg), and a poorly relaxing LES, with a residual pressure greater than 8 mm Hg. It is well understood, though, that as many as 50% of patients with the clinical diagnosis of achalasia do not have a hypertensive LES; however, the diagnosis does require aperistalsis and a poorly relaxing LES (Figure 3.4). Recent studies have attempted to subclassify achalasia on the basis of findings from high-resolution manometry and Clouse plots. As a result, interpretation of manometry relies much more on recognition of color plots than of waveforms. The precise role of classifications based on these plots is currently being studied.

Treatment

Treatment of achalasia aims at pharmacologic relaxation or mechanical disruption of the LES. Because of the rarity of achalasia, few randomized controlled trials have defined the best treatment strategy. Several medications have been used in the treatment of achalasia, including nitrates, calcium channel blockers, and nitric oxide donors (sildenafil), in an attempt to either facilitate LES relaxation or augment esophageal peristalsis (or both). Adverse effects and lack of efficacy have limited the common use of these medications for achalasia.

Injection of botulinum toxin into the LES is an appealing strategy because it is safe and easily performed. Studies have shown that this treatment provides excellent short-term symptomatic improvement. However, repeated injections are usually required because of the short-term activity of botulinum toxin. This is complicated further by the development of antibodies that make repeated injections increasingly ineffective. Also, there is evidence that injection of botulinum toxin into the LES is associated with increased difficulty in performing esophagomyotomy later. For this reason, many clinicians reserve the use of botulinum toxin for

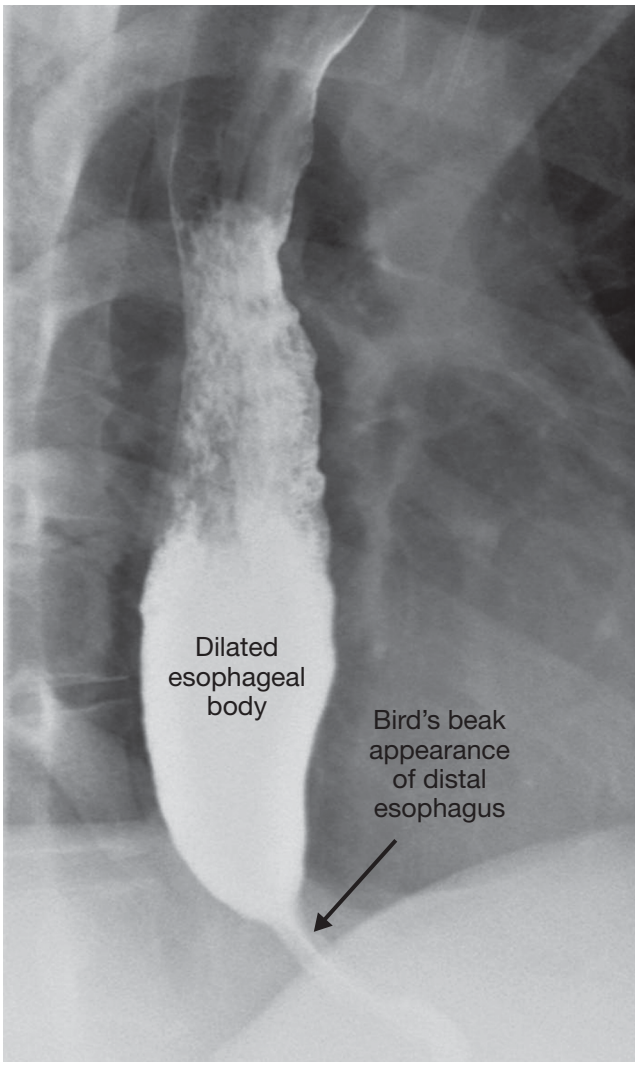

Figure 3.3. Achalasia on Esophagography. Barium esophagram from a patient with achalasia shows a dilated esophagus with a "bird's beak" narrowing at the lower esophageal sphincter.

patients who are of extremely advanced age or who have severe comorbidities that preclude treatment with pneumatic balloon dilation or esophagomyotomy because of the associated risks.

Dilation of the LES in patients with achalasia should be directed at disrupting the muscularis propria. Bougienage or standard balloon dilation typically is ineffective for achalasia, but pneumatic balloon dilation with a rigid balloon across the LES has been shown to be effective and inexpensive. The primary drawbacks of pneumatic dilation are the risk of esophageal perforation (approximately 2%) and lack of durability, compared with surgical treatment, according to most studies.

Esophagomyotomy or Heller myotomy allows for more precise splitting of the LES directly. A longitudinal incision is initiated on the gastric side approximately 2 cm distal to the gastroesophageal junction and extended proximally 7 cm above the junction. Over the past 20 years, this procedure has been performed safely and successfully with laparoscopy. Long-term studies (10 years of follow-up) have shown that surgical myotomy produces symptomatic relief in 80% to 85% of patients.

In nearly 50% of patients who have a modified Heller myotomy, gastroesophageal reflux disease develops; in some patients, erosive esophagitis, stricture, or Barrett esophagus develop. A prospective randomized clinical trial of myotomy with and without Dor (or anterior) fundoplication showed that patients with the Dor procedure had much less gastroesophageal reflux, as assessed with 24-hour esophageal pH testing, than those without fundoplication (9% vs 48%). This has led to the common practice in most centers of coupling the modified Heller myotomy with fundoplication.

The roles of pneumatic dilation and surgery are still being evaluated. Only 2 randomized prospective trials have compared esophagomyotomy with pneumatic dilation. These studies showed that both treatments were equally effective in relieving symptoms initially, but in the study with the longer follow-up, patients who had esophagomyotomy had fewer recurrent symptoms than those who had pneumatic dilation.

Several studies have reported long-term outcomes for patients with achalasia. Overall, there is no difference in life expectancy or mortality for patients with treated achalasia than for the general population. However, there is clear evidence that patients with achalasia (treated or untreated) are at increased risk for esophageal squamous cell carcinoma. There is no consensus about screening; however, most experts recommend endoscopy at least once in the decade following the diagnosis of achalasia. Furthermore, if new or worsening dysphagia develops in a patient with achalasia, upper endoscopy should be performed.

Nonspecific Esophageal Dysmotility

Hypercontractile Esophageal Disorders

Diffuse Esophageal Spasm

Diffuse esophageal spasm is likely a rare disease. The true prevalence is uncertain because it can be difficult to diagnose. The typical symptom complex for this condition is intermittent chest pain (it may radiate to the back or throat) associated with dysphagia. The pathophysiology of diffuse esophageal spasm is poorly understood, but the condition may reflect a forme fruste (ie, an incomplete form) of achalasia. Over the past several decades, it has become clear that *diffuse* esophageal spasm is a misnomer because the spastic component affects only the smooth muscle in the distal two-thirds of the esophagus. A small study of patients with diffuse esophageal spasm suggested that there may be dysfunction in the endogenous synthesis or degradation of nitric oxide. This finding explains why nitrates often provide benefit in the treatment of diffuse esophageal spasm.

The hallmark of diffuse esophageal spasm is the presence of simultaneous contractions in more than 20% of swallows. There must be at least 1 swallow with peristalsis (in distinction from achalasia). Often, contractions are repetitive (≥3 peaks) and the distal peristaltic duration is increased (>6 seconds) (Figure 3.5). Barium esophagram findings are variable in diffuse esophageal spasm. Classically, severe tertiary contractions can produce a "corkscrew" esophagus (Figure 3.6). However, because the results of radiographic studies may be normal in diffuse esophageal spasm, normal findings do not rule out the diagnosis. The diagnosis is made on the basis of clinical symptoms and manometric findings.

Nutcracker Esophagus

The term *nutcracker esophagus* is used to describe the manometric finding of high-pressure peristaltic contractions in the distal

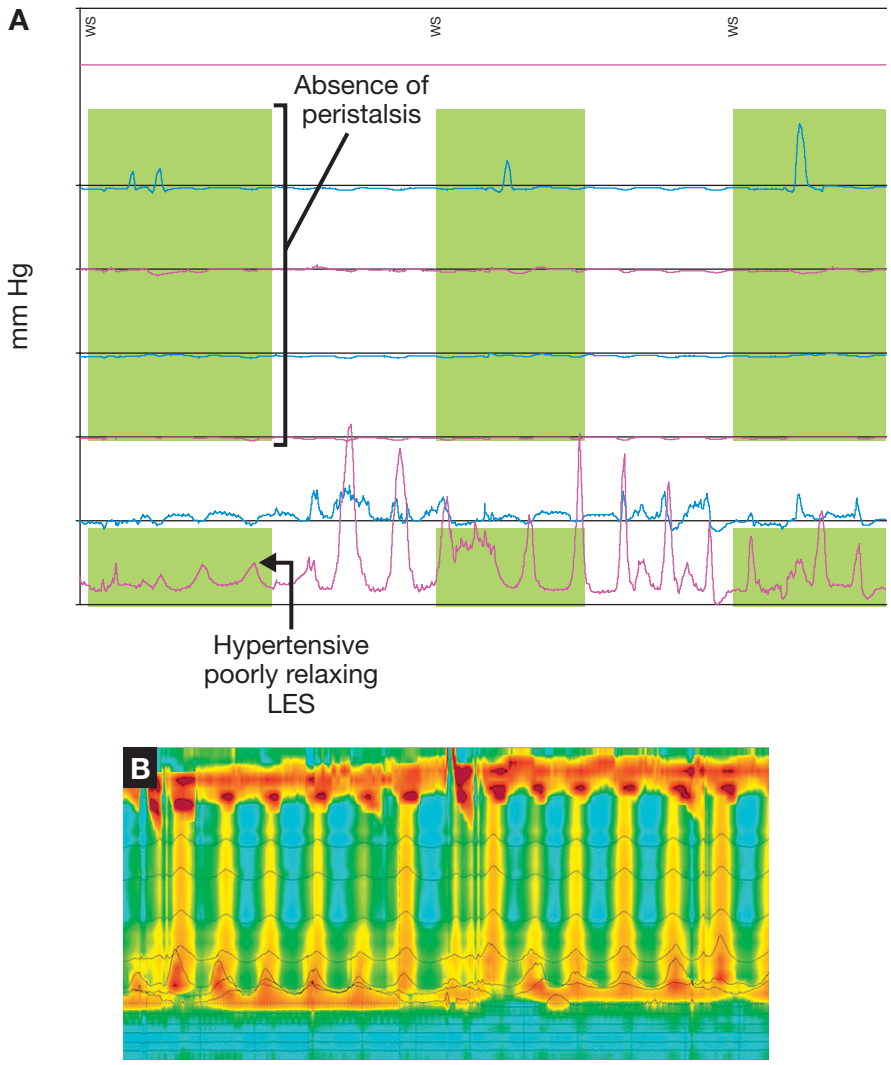

Figure 3.4. Achalasia on Esophageal Manometry. A, Esophageal manometry from a patient with achalasia. Note that peristalsis is absent and that the lower esophageal sphincter (LES) does not fully relax. WS indicates wet swallow. B, High-resolution manometry Clouse plot from a patient with type II achalasia with isobaric pressurizations.

esophagus, with an average amplitude of pressure higher than 220 mm Hg on 10 or more liquid swallows and with otherwise normal peristalsis. Recently, it has been renamed *jackhammer esophagus* by authors of the Chicago Classification. Nutcracker esophagus was first described more than 3 decades ago, and since that time, there has been considerable controversy about the association of this manometric finding with symptoms. In a study that examined the manometric findings from patients with unexplained chest pain, nutcracker esophagus was the most common abnormal finding, occurring in 12% of patients. Many patients with the manometric finding of nutcracker esophagus do not have chest pain. In an unpublished study at Mayo Clinic, 15% of asymptomatic patients who underwent esophageal manometry before 24-hour impedance pH testing met the manometric criteria for nutcracker esophagus.

A study with 24-hour ambulatory esophageal manometry found that patients who had nutcracker esophagus or diffuse esophageal spasm according to stationary manometry frequently switched patterns over 24 hours, suggesting that nutcracker esophagus may be a marker for esophageal spasm. With the use of high-frequency intraluminal ultrasonography to examine patients who have nutcracker esophagus, asynchrony was found in the contractions of the circular and longitudinal muscle layers of the esophagus, and this was reversed with atropine, suggesting that the manometric abnormality may be due to a hypercholinergic state. Nevertheless, the etiology and specific treatment of this manometrically defined disease is still unclear.

Hypertensive LES

The manometric finding of a hypertensive LES (LES resting pressure >45 mm Hg) without other abnormalities denotes a primary esophageal motility disorder of the hypercontractile subtype. Some patients with a hypertensive LES also have a poorly relaxing LES. As many as 50% of patients with a hypertensive LES also have high-amplitude distal esophageal peristalsis consistent with nutcracker esophagus. Treatment should not be initiated for this manometric finding unless there are other supporting objective and symptomatic criteria to support an associated dysfunction.

Treatment

Because the pathophysiology of discoordinated and hypercontractile esophageal motility disorders is poorly understood and

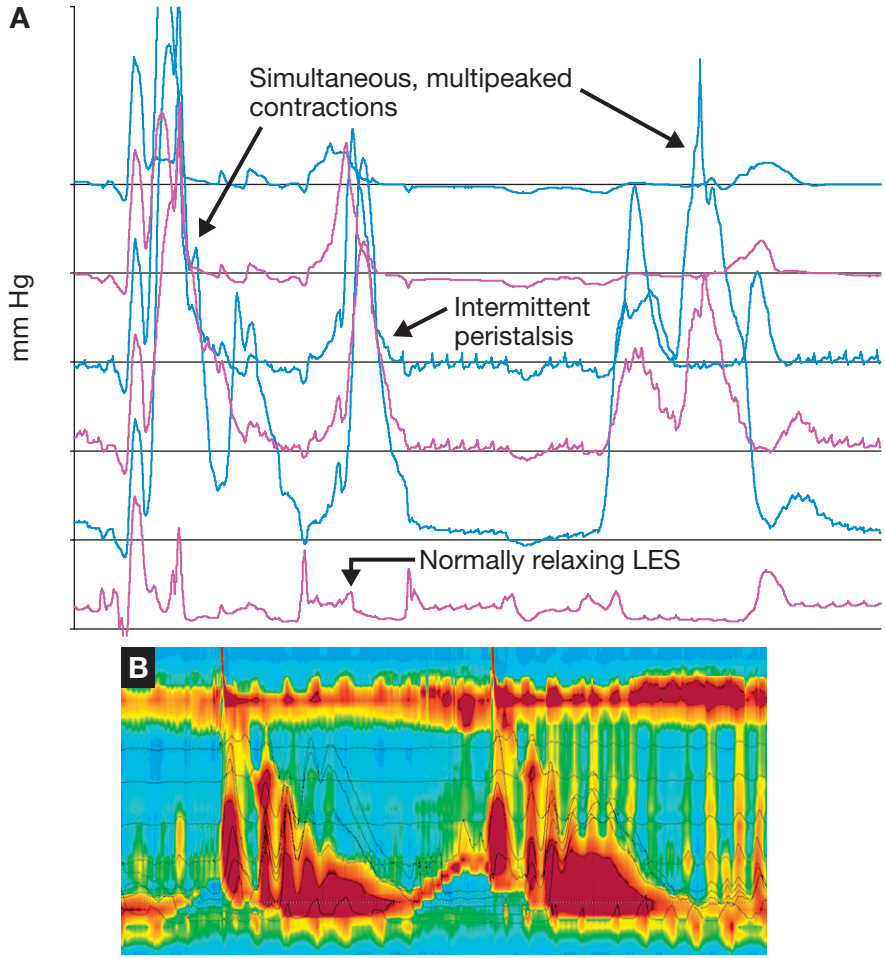

Figure 3.5. Diffuse Esophageal Spasm on Esophageal Manometry. A, Esophageal manometry from a patient with diffuse esophageal spasm. Note the simultaneous, multipeaked contractions of prolonged duration with intermittent peristalsis. LES indicates lower esophageal sphincter. B, High-resolution manometry Clouse plot from a patient with diffuse esophageal spasm with high-amplitude simultaneous contractions.

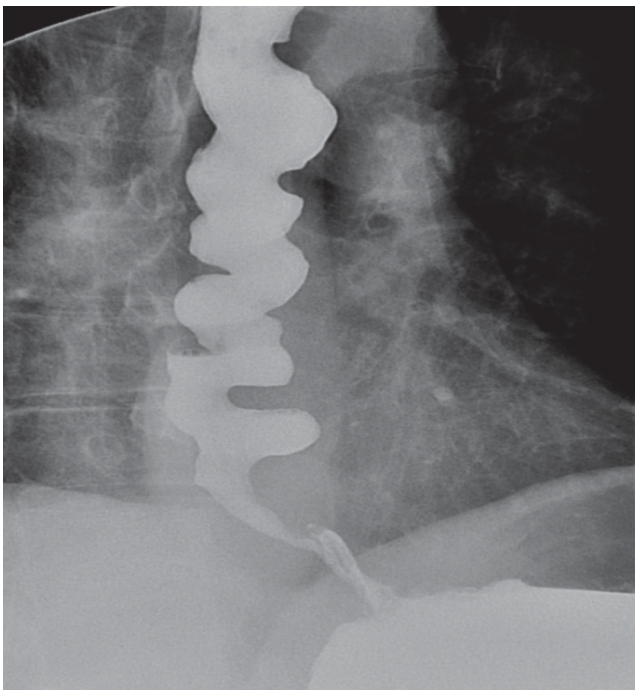

Figure 3.6. Diffuse Esophageal Spasm on Esophagography. Barium esophagram showing "corkscrew" esophagus in a patient with diffuse esophageal spasm.

the association with symptoms is unclear, only a few appropriately designed and powered studies have evaluated therapy for these disorders. Generally, the medications that have been used with success have been used to treat all these disorders (ie, diffuse esophageal spasm, nutcracker esophagus, and hypertensive LES).

Both nitrates and calcium channel blockers have some effect. Diltiazem was studied in a randomized, double-blind crossover study (60-90 mg 4 times daily), and, compared with placebo, diltiazem relieved chest pain in patients with nutcracker esophagus. There have been anecdotal reports of the usefulness of nitrates and anticholinergic agents, but these have not been studied in a controlled trial.

Gastroesophageal reflux disease has been suggested to have a role in spastic disorders of the esophagus, and some small studies have shown symptomatic improvement with proton pump inhibitor therapy.

Trazodone (100-150 mg daily) and imipramine (50 mg daily) have been shown to be effective in improving chest pain in patients with esophageal motility disorders, likely by modifying visceral sensation. This group of patients can be classified into those with hypersensitive esophagus or those with functional dysphagia. Sildenafil inactivates nitric oxide–stimulated cyclic guanosine monophosphate and, as a result, can cause the LES to relax. Several investigators have studied the effect of sildenafil, at a dose of 50 mg, on the LES and have found that it relieved symptoms in a group of 11 patients who had nutcracker esophagus or diffuse esophageal spasm.

Injection of botulinum toxin also has been studied in this group of patients. The largest series included 29 patients who had chest pain or dysphagia and the diagnosis of a spastic esophageal motility disorder (diffuse esophageal spasm, hypertensive LES, or nutcracker esophagus). The patients received 100 units of botulinum toxin injected at the Z line (given as 5 circumferential injections, with 20 units/mL in each); 70% of the patients had some improvement and nearly 50% had complete relief.

Patients who have profound symptoms (eg, severe dysphagia associated with weight loss or aspiration associated with severe dysphagia) refractory to other treatments may benefit from long esophageal myotomy.

Hypocontractile Esophageal Disorders

Hypocontractile esophageal disorders are characterized by hypotensive LES either alone or in combination with increased low-amplitude peristalsis (>50% wet swallows and low mean distal peristaltic amplitude of <30 mm Hg). It is of utmost importance that hypocontractile esophagus not be confused with achalasia: Both may have aperistalsis (this is uncommon), but achalasia also has a poorly relaxing LES; in hypocontractile esophagus, the LES relaxes normally or is hypotensive at rest (or both) (Figure 3.7).

The most common causes of hypocontractile disorders of the esophagus are systemic smooth muscle myopathies such as amyloidosis and connective tissue diseases (eg, scleroderma, CREST [calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia] syndrome, and mixed connective tissue disease). Muscular dystrophies and familial visceral myopathies also can be associated with ineffective motility.

Patients often present with dysphagia but also may have symptoms typical of gastroesophageal reflux disease. The hypotensive LES promotes gastroesophageal reflux disease, and dysphagia in these patients may be due to the underlying motility disorder, although it may be due also to peptic stricture. If a patient has a known hypomotility disorder and presents with worsening dysphagia, the esophagus should be assessed endoscopically.

Little can be done to treat hypocontractile esophageal disorders. Most patients require acid-suppressing medications for

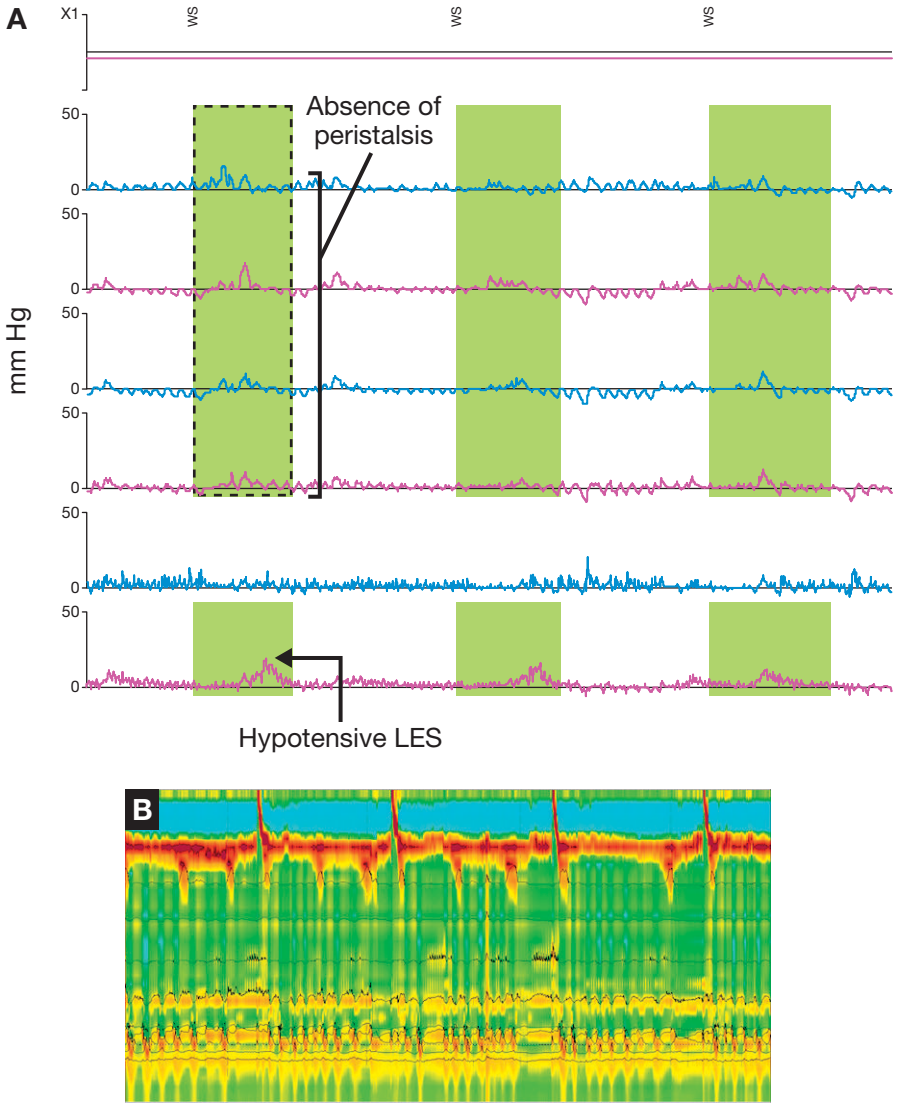

Figure 3.7. Aperistalsis on Esophageal Manometry. A, Esophageal manometry from a patient with scleroderma showing the absence of peristalsis by a hypotensive and relaxing lower esophageal sphincter (LES) (in distinction from achalasia). WS indicates wet swallow. B, High-resolution manometry Clouse plot from a patient with scleroderma and aperistalsis.

gastroesophageal reflux disease and its complications. Otherwise, the recommendation of good swallowing technique (small bites, well-chewed food, sipping liquid after bites, and focused swallowing) is the only useful intervention.

Postfundoplication Motor Disorders

Several abnormalities are detected with esophageal manometry after fundoplication. The resting LES pressure may be higher than normal, or the LES may not relax normally in response to swallowing. In severe cases, the manometric findings can appear similar to those of achalasia, with aperistalsis and a hypertensive, poorly relaxing LES. For patients with dysphagia and these findings, dilation of the distal esophagus is sometimes helpful. If not, and if dysphagia is profound, revision of the fundoplication may be warranted. In most patients who have esophageal body motility changes with a tight fundoplication, abnormalities are reversed after the fundoplication has been revised.

Box 3.1. Indications for Esophageal Manometry

Esophageal manometry clearly indicated

- Manometry is indicated to establish the diagnosis of dysphagia when a mechanical obstruction cannot be found on endoscopy or barium esophagram
- Manometric techniques are indicated for placement of intraluminal devices (eg, pH probes) when positioning is dependent on the relationship to functional landmarks, such as the lower esophageal sphincter
- Manometry is indicated for the preoperative assessment of patients being considered for antireflux surgery if there is any question of an alternative diagnosis, especially achalasia

Esophageal manometry possibly indicated

- Manometry is possibly indicated for the preoperative assessment of peristaltic function in patients being considered for antireflux surgery
- Manometry is possibly indicated to assess symptoms of dysphagia in patients who have undergone either antireflux surgery or treatment for achalasia

Esophageal manometry not indicated

- Manometry is not indicated for making or confirming a suspected diagnosis of gastroesophageal reflux disease
- Manometry should not be routinely used as the initial test for chest pain or other esophageal symptoms, because of the low specificity of the findings and the low likelihood of detecting a clinically significant motility disorder

Adapted from Pandolfino JE, Kahrilas PJ; American Gastroenterological Association. American Gastroenterological Association medical position statement: clinical use of esophageal manometry. Gastroenterology. 2005 Jan;128(1):207-8. Used with permission.

Indications for Esophageal Manometry

Esophageal manometry can be a very useful diagnostic tool in the right patient setting. It is important, however, to recognize its appropriate use. The American Gastroenterological Association has provided guidelines for the indications of esophageal manometry in clinical practice (Box 3.1).

Summary

The normal function of the esophagus is to transfer food and liquid boluses from the mouth to the stomach and to prevent stomach contents from refluxing upward. Normal esophageal motility is required for these functions. Motility disorders of the UES produce oropharyngeal dysphagia, a symptom complex that is clinically distinct from esophageal dysphagia. Of the different esophageal motility disorders, achalasia is the one best established, with clearly defined and effective treatments. Most other esophageal motility disorders have questionable associations with clinical symptoms and few effective treatment options.

Suggested Reading

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Questions and Answers

Questions

Abbreviations used:

ACG, American College of Gastroenterology
ASGE, American Society for Gastrointestinal Endoscopy
BE, Barrett esophagus
CT, computed tomography
EGD, esophagogastroduodenoscopy
GERD, gastroesophageal reflux disease
LES, lower esophageal sphincter
PEG, percutaneous endoscopic gastrostomy
PPI, proton pump inhibitor
UES, upper esophageal sphincter

Multiple Choice (choose the best answer)

I.1. **A 51-year-old man complains of heartburn and acid regurgitation for 2 years. He has dysphagia for solids and points to the lower sternum as the site where he senses food gets stuck. He has not lost weight. His heartburn responds to antacids. Complete blood cell count results are normal. Which of the following tests is most appropriate?**

a. Ambulatory esophageal pH-impedance test
b. Esophageal manometry
c. Nissen fundoplication
d. Upper endoscopy
e. PPI trial

I.2. **A 38-year-old woman presents with a 1-year history of increasingly frequent and severe heartburn and acid regurgitation, especially when she bends over. She has cold hands and feet that change color when exposed to colder temperatures. She is not overweight and is a nonsmoker. Her symptoms of heartburn have responded to a once-daily PPI. Upper endoscopy findings are negative. Which of the following tests is most likely to have positive results?**

a. *Helicobacter pylori* stool antigen
b. IgA tissue transglutaminase antibody
c. Antinuclear antibody
d. Anti–parietal cell antibody
e. Antimitochondrial antibody

I.3. **A 35-year-old woman presents with a 5-year history of recurrent central chest discomfort that is burning in character and occurs several times daily. It has been unresponsive to treatment that has included nitroglycerin and 8 months of omeprazole, 40 mg twice daily, which she is still taking. One year ago, the results of a cardiac evaluation and an EGD were normal. What is the next best step?**

a. Refer her for a surgical evaluation
b. Refer her for a psychiatric evaluation
c. Change the PPI
d. Repeat the EGD
e. Perform an ambulatory esophageal pH-impedance test

I.4. **A 34-year-old man has a 6-month history of heartburn and regurgitation that is notable most evenings. He denies weight loss, dysphagia, or abdominal pain. He is moderately overweight (body mass index, 29). He has no other illnesses. Which of the following is most appropriate at this time?**

a. Antacids as needed with lifestyle modifications
b. Daily PPI
c. Barium esophagram
d. EGD with esophageal biopsies
e. Ambulatory esophageal pH-impedance test

I.5. **A 22-year-old man presents with a history of food impaction that had passed spontaneously. He has had multiple similar**

episodes in the past. He also has a history of weekly heartburn. He presents for upper endoscopy, and the examination findings are normal. Which of the following should be done next?

a. Treat with PPI therapy alone
b. Take 5 biopsies from the distal esophagus
c. Dilate the esophagus with a 15-mm Savary dilator
d. Take 2 to 4 biopsies from the distal and proximal esophagus
e. Provide reassurance alone

I.6. A 60-year-old white man is referred to you for 20 years of typical heartburn that often disturbs his sleep. He has used antacids and over-the-counter histamine$_2$-blockers with moderate but temporary relief. His primary doctor has prescribed once-daily omeprazole, which he takes at night before bed. This has not helped. He is overweight and has had a long history of diarrhea-predominant irritable bowel syndrome. On endoscopy, he has grade C (Los Angeles classification) reflux esophagitis but no endoscopic changes to suggest BE. Which of the following is most likely to help his symptoms?

a. Perform Nissen fundoplication
b. Prescribe a histamine$_2$-blocker at night
c. Switch omeprazole to twice daily dosing before meals
d. Elevate the head of his bed
e. Refer for sleep apnea testing

I.7. A 62-year-old white man reports a history of gastroesophageal reflux for the past 12 years. He states that symptoms are controlled with a PPI once daily, and he has no alarm symptoms. He is centrally obese, but the remainder of the physical examination findings are normal. Which of the following statements is most accurate regarding screening for BE?

a. All professional gastrointestinal societies strongly recommend screening for BE in the general population
b. Central obesity, male sex, white ethnicity, and chronic reflux symptoms increase the risk that BE will be found on endoscopy
c. Screening for BE has been shown in prospective studies to decrease mortality due to esophageal adenocarcinoma
d. Most patients with chronic (>10 years) reflux symptoms have evidence of long-segment BE at endoscopy
e. Screening for BE, followed by surveillance of all patients (regardless of dysplasia grade), is cost-effective

I.8. A 68-year-old man has gastroesophageal reflux that is well controlled with once-a-day PPI. Recently, he underwent his first upper endoscopy, which showed long-segment BE with no dysplasia. Which of the following would be the most appropriate recommendation?

a. Upper endoscopy with surveillance biopsies in 1 year
b. Endoscopic ultrasonography with additional biopsies in 3 months
c. Referral for fundoplication
d. Twice-daily dosing of the PPI
e. Endoscopic ablative therapy of the Barrett segment

I.9. A 72-year-old man undergoes upper endoscopy for surveillance of known BE. Endoscopic evaluation shows a 3-cm segment of BE, with a 1-cm nodular lesion in the distal esophagus; targeted biopsies of the nodule show high-grade dysplasia. His medical history is remarkable for diabetes mellitus and coronary artery disease. Physical examination is notable for a body mass index of 39. He expresses the desire to avoid surgery and is interested in pursuing endoscopic therapy. Which of the following statements regarding his management is correct?

a. Endoscopic mucosal resection is superior to biopsy alone for assessment of the nodular lesion in the distal esophagus
b. The survival of patients treated surgically is superior to that of those treated endoscopically
c. Surgical mortality and morbidity are independent of hospital or surgical volume
d. Recurrence of neoplasia is negligible after endoscopic therapy
e. Radiofrequency ablation should be performed before assessment of the nodular lesion by endoscopic mucosal resection

I.10. A 62-year-old man is referred with a new diagnosis of long-segment BE with low-grade dysplasia that was discovered recently during upper endoscopy. His reflux symptoms are well controlled with a PPI, and there is no evidence of esophagitis or visible lesions on endoscopy. What is the most appropriate next step in the management of this patient?

a. Increase the PPI dosing to twice daily and repeat upper endoscopy in 3 months
b. Perform endoscopic ablative therapy
c. Refer for esophagectomy
d. Enroll the patient in a chemoprevention trial
e. Have an expert gastrointestinal pathologist confirm the diagnosis of low-grade dysplasia and ask the patient to return for endoscopic surveillance in 6 months

I.11. A 60-year-old man presents with new-onset dysphagia and is found to have a 3-cm mass in the distal esophagus, with biopsies confirming adenocarcinoma. Staging with positron emission tomography and CT of the chest and abdomen show no metastatic lesions. Endoscopic ultrasonography shows a T2N1 lesion. Initially, the patient's body weight decreased by 4.5 kg, but his weight has now stabilized. What would be the suggested course for treatment after staging?

a. Endoscopic therapy with endoscopic mucosal resection
b. Neoadjuvant chemoradiotherapy, followed by surgery
c. Esophagectomy, followed by adjuvant chemotherapy
d. Esophageal stent placement for palliation of dysphagia
e. Placement of a PEG tube for nutritional support

I.12. A 65-year-old man with long-segment BE returns to the clinic after surveillance endoscopy that showed low-grade dysplasia confirmed by an expert gastrointestinal pathologist. He has a 3-cm segment, without any nodularity, and has no family history of esophageal malignancy. What is the appropriate next step in management of this patient?

a. Esophagectomy
b. Endoscopic mucosal resection
c. Fundoplication
d. Surveillance endoscopy in 1 year
e. No follow-up needed

I.13. What is the main inhibitory neuropeptide for relaxation of the LES?

a. Substance P
b. Acetylcholine
c. Gastrin
d. Nitric oxide

I.14. According to the Chicago Classification, what characterizes the esophageal body in type II achalasia?

a. Isobaric pressurizations
b. No discernible pressurizations
c. Multiple spontaneous and repetitive pressurizations
d. Prolonged pressurizations

I.15. For the diagnosis of achalasia, which manometric finding is most sensitive?

a. Elevated integrated residual pressure
b. Elevated LES pressure
c. Incomplete LES relaxation
d. Prolonged distal latency

I.16. To what is the pathophysiology of a Zenker diverticulum most closely related?

a. Elevated pharyngeal pressures with deglutition
b. Loss of compliance of the UES
c. Low UES pressure
d. Poor coordination between pharyngeal contraction and UES opening

I.17. What is the treatment of choice for a 1-cm Zenker diverticulum?

a. Cricopharyngeal myotomy
b. Diverticulectomy
c. Diverticulopexy
d. Cricopharyngeal myotomy and diverticulectomy

I.18. Which disorder would *not* lead to esophageal aperistalsis?

a. Scleroderma
b. Achalasia
c. Amyloidosis
d. Dermatomyositis

Answers

I.1. Answer d.
This patient has a recent history of dysphagia for solids, and even though he has not lost weight, this constitutes an alarm symptom. The patient's identification of the distal sternum as the site of holdup indicates a distal cause. Ambulatory pH studies or manometry are not indicated at this time. A barium test could be an alternative option as a first step, with dysphagia being the only symptom indication for a barium study in GERD.

I.2. Answer c.
This patient has the recent onset of typical features of severe GERD, yet she lacks the typical risk factors for GERD. She describes Raynaud phenomenon, and she most likely has an underlying connective tissue disease, where a nonspecific antinuclear antibody may be detected. Esophageal manometry may reveal a hypoperistaltic esophagus and diminished resting LES pressure.

I.3. Answer e.
There is little point in repeating her previously negative EGD. Changing the PPI or increasing the PPI dose is unlikely to have any effect given the current dose and frequency. For this patient with noncardiac chest pain, it is important to make a positive diagnosis, and ambulatory pH-impedance testing provides the most accurate test for determining whether frequent chest pain is due to GERD.

I.4. Answer b.
This patient has typical symptoms of uncomplicated GERD. He has no alarm symptoms to justify an EGD, and there are no indications for biopsies of his esophagus. A barium esophagram is not indicated for the diagnosis of GERD unless the patient has dysphagia, in which case it could be considered. While antacids and lifestyle changes are laudable, they are unlikely to resolve his symptoms.

I.5. Answer d.
This young man has symptoms highly suggestive of eosinophilic esophagitis. While the finding of increased eosinophils is not specific for eosinophilic esophagitis, which can respond to PPI therapy, we do not know whether he has esophageal eosinophilia. Biopsies should not be limited to the distal esophagus since the eosinophilic esophagitis may be proximal. Although empirical dilation was advocated for dysphagia in the past, that was before eosinophilic esophagitis was recognized as an important cause of food impaction. Dilation could be used in eosinophilic esophagitis patients who have either severe strictures or moderate strictures unresponsive to conservative therapies. In this case, no stricture was seen.

I.6. Answer c.
This patient not only has the classic symptoms of GERD but also confirmation of the diagnosis with endoscopic delineation of reflux esophagitis. His current therapy is inadequate, however, which may be related to the current dose. Taking the PPI on an empty stomach with a meal within 30 to 60 minutes will optimize the acid suppression. Oral PPIs are quite effective at healing esophagitis and relieving symptoms. It would be premature to consider surgery at this point.

I.7. Answer b.
Central obesity (as determined by waist circumference >80 cm), male sex, white ethnicity, and chronic reflux symptoms (>5-10 years) are predictive of increased risk of BE being found on endoscopic evaluation. Currently, screening for BE in the general population is not recommended by any national gastrointestinal society. For patients with chronic reflux symptoms, screening may be considered on an individual basis, according to the 2008 guidelines of the ACG and the ASGE. This lack of enthusiasm for screening is based on the absence of evidence from prospective studies that demonstrates survival benefit from screening, the relatively poor sensitivity and specificity of reflux symptoms in predicting or excluding the presence of BE, the absence of widely applicable tools for screening, and the current limitations of surveillance. Only 10% of patients with chronic reflux have BE at endoscopy, and as many as 40% to 50% of patients who have BE (and esophageal adenocarcinoma) do not experience frequent reflux symptoms. Modeling studies (based on assumptions) have shown that screening, followed by surveillance, in patients with dysplasia may be cost-effective. However, surveillance for patients without dysplasia is prohibitively expensive.

I.8. Answer a.
For the diagnosis of BE without dysplasia, the current recommendation is follow-up endoscopy within 12 months to exclude prevalent dysplasia that may have been missed on initial endoscopy, followed by surveillance every 3 to 5 years, assuming no dysplasia is found on follow-up endoscopy. The risk of progression in patients with BE who undergo fundoplication to control reflux is not lower than for those who receive medical therapy with PPIs to control reflux. This was shown in a robust meta-analysis. The current goal of therapy with PPIs for patients with BE is symptom control. If patients have adequate symptom control with once-daily therapy, there is no indication to increase the dosage to twice daily. Currently, endoscopic ablative therapy is not recommended for patients without dysplasia. Follow-up endoscopy with additional biopsies and endoscopic ultrasonography would be appropriate for patients with high-grade dysplasia.

I.9. Answer a.
Endoscopic mucosal resection allows precise staging of nodular lesions in BE by providing both the mucosa and the submucosa for histopathologic study. Endoscopic mucosal resection is known to increase the grade of dysplasia (from high-grade dysplasia to carcinoma) in up to 40% of patients referred for endoscopic therapy and allows mucosal and submucosal invasion to be distinguished. Margins of endoscopic mucosal resection specimens

can be assessed; they correlate well with esophagectomy pathology findings. Surgical mortality correlates well with hospital and surgical volume; higher volumes are associated with lower mortality rates. A retrospective cohort study showed that overall 5-year survival of patients with high-grade dysplasia treated with endoscopic therapy was comparable to that of those treated surgically. Unlike esophagectomy, endoscopic therapy requires multiple procedures to achieve remission or eradication of dysplasia and intestinal metaplasia, followed by endoscopic surveillance to detect and treat recurrences. Recurrence of dysplasia has been reported for 17% to 21% of patients. Most of these are treatable endoscopically if follow-up is appropriate.

I.10. Answer e.
The diagnosis of BE with low-grade dysplasia should be confirmed by a gastrointestinal pathologist (given the poor interobserver agreement between community and academic pathologists in the diagnosis of dysplasia arising in BE), followed by repeat endoscopy with 4-quadrant surveillance biopsies every 2 cm within 6 months to exclude advanced prevalent dysplasia.

In a multicenter cohort of patients with low-grade dysplasia followed over 3 years, the natural history of low-grade dysplasia was characterized by reversion to no dysplasia in the majority of patients, stability at low-grade dysplasia in one-third, and progression to high-grade dysplasia or adenocarcinoma in 10%. A recent meta-analysis estimated the rate of progression in low-grade dysplasia at 17 per 1,000 patient-years of follow-up, compared with 6 per 1,000 patient-years of follow-up in non-dysplastic BE, and 66 per 1,000 patient-years of follow-up in high-grade dysplasia. Currently, endoscopic surveillance is recommended for patients with low-grade dysplasia. Ablation, if considered, should be in research protocols. Esophagectomy is not recommended for patients with low-grade dysplasia (but is a treatment option for those with high-grade dysplasia). Currently, chemoprevention for BE is not standard clinical practice.

I.11. Answer b.
Neoadjuvant chemoradiotherapy, followed by esophagectomy, has been shown to confer a modest survival benefit for patients with locally advanced esophageal adenocarcinoma (T3 or N1), in comparison with esophagectomy alone. The presence of dysphagia usually indicates invasive disease that is not amenable to local endoscopic therapy (which, thus, is appropriate for only mucosally confined disease, given the low risk of metastatic lymph node involvement). With the absence of metastatic disease and the stability of the patient's weight, esophageal stent placement is not indicated at this time, nor is placement of a PEG tube, which could be indicated for malnourished patients (>10% loss of body weight) with severe limitation in caloric intake.

I.12. Answer d.
The appropriate next step would be to recommend surveillance endoscopy in 1 year. Esophagectomy and endoscopic mucosal resection are appropriate for patients with high-grade dysplasia with a visible lesion. Fundoplication does not confer any advantage over medical therapy for reflux in terms of decreasing the risk of progression to adenocarcinoma.

I.13. Answer d.
Nitric oxide is the main inhibitory neurotransmitter throughout the gastrointestinal tract, including the LES. Substance P and acetylcholine are both excitatory neuropeptides in the gastrointestinal tract. Gastrin was once thought to affect LES tone but only in supraphysiologic doses.

I.14. Answer a.
Type II achalasia is represented by isobaric pressurizations in response to swallows. Type I is represented by no discernable pressurizations, and type III by spontaneous and repetitive pressurizations (a "spastic" pattern). Prolonged pressurizations may be found in diffuse esophageal spasm, in type III achalasia, and, if peristaltic, in nutcracker esophagus.

I.15. Answer a.
In the past, the diagnosis of achalasia was based on the elevation of LES pressure or incomplete relaxation of the LES (or both), but the new analysis, integrated residual pressure, is more accurate and specific for measuring both of these functions in achalasia. Prolonged distal latency is opposite what one would expect in achalasia, where the loss of inhibitor fibers leads to shortened latency.

I.16. Answer b.
The pathophysiology of a Zenker diverticulum is generally thought to result from replacement of the sphincter by fibrotic tissue, leading to a loss of compliance. UES pressures are not consistently seen in patients with a Zenker diverticulum, nor is low pressure. Similarly, this is not a disease of incoordination.

I.17. Answer a.
Cricopharyngeal myotomy is essential to any surgical approach to a Zenker diverticulum. Repair of the diverticulum alone, as in diverticulectomy or diverticulopexy, would result in a recurrent diverticulum. If the diverticulum is small, only a myotomy is needed.

I.18. Answer d.
Achalasia, scleroderma, and amyloidosis are all diseases that, through a myogenic cause or a neurogenic cause (or both), lead to complete smooth muscle dysfunction of the esophagus. Since dermatomyositis involves only striated muscle (unless there is an overlap syndrome), the peristaltic function of the distal two-thirds of the esophagus is preserved.

II

Stomach

4

Peptic Ulcer Disease

STEPHANIE L. HANSEL, MD, MS

A *peptic ulcer* is a persistent 5-mm or larger break in the gastrointestinal mucosa of the stomach or duodenum that penetrates through the muscularis mucosa. At endoscopy, an ulcer should be readily apparent with perceivable depth. Smaller, shallower mucosal breaks represent erosions. Most peptic ulcers are due to *Helicobacter pylori* (HP) infection or the administration of nonsteroidal antiinflammatory drugs (NSAIDs). The term *peptic ulcer disease* (PUD) refers to ulceration that depends in part on the acid and peptic (ie, with pepsins) activity of gastric juice. Most peptic ulcers occur in the stomach or duodenal bulb.

Epidemiology

PUD is a common condition worldwide. The incidence has been decreasing in developed countries, most likely the result of a decreasing incidence of HP infections. The worldwide annual incidence of PUD ranges from 0.10% to 0.19%. The lifetime prevalence of PUD in the United States may be as high as 10% among the general population and up to 20% for persons infected with HP.

Pathophysiology

Peptic ulcers occur when there is an imbalance between processes that damage the gastrointestinal mucosa and mechanisms that protect it. Acid secretion occurs through gastric proton pumps located in parietal cells. These are hydrogen-potassium-ATPase pumps, which use adenosine triphosphate to transport hydrogen across the cell membrane into the gastric lumen and to transport potassium in the opposite direction. At rest, these pumps are located intracellularly. Stimulation of parietal cells by a combination of acetylcholine (vagus nerve), gastrin (antral G cells), and histamine (enterochromaffin-like [ECL] cells) translocates the proton pumps to the apical secretory canalicular (luminal) membrane, where they become functional (Figure 4.1). During the cephalic phase of meal-stimulated acid secretion, vagal activity stimulates ECL cells, G cells, and parietal cells. During the gastric phase, distention of the stomach augments vagal output, and short peptides, amino acids, and calcium, as well as alkaline pH, stimulate gastrin release by G cells. Gastrin release is inhibited by a gastric pH less than 3. Acid pH also stimulates somatostatin-producing D cells in the antrum and body of the stomach, with somatostatin inhibiting gastrin release from G cells and acid secretion from parietal cells.

The normal mucosal defense mechanisms against gastric acid include the surface mucous layer; the secretion of bicarbonate, mucus, and phospholipid by gastroduodenal epithelial surface mucous cells; the epithelial barrier; mucosal blood flow; epithelial cell restitution; and epithelial cell renewal (Figure 4.2). Many of these defense mechanisms are prostaglandin-dependent.

Etiology

As stated above, the most common causes of PUD are HP infection and the use of NSAIDs, including low-dose aspirin. Less common causes of PUD include hypersecretory states, viral infections (cytomegalovirus and herpes simplex virus 1 infections), drug exposure (cocaine), ischemia, radiotherapy, and infiltrative disorders (malignancy, sarcoidosis, Crohn disease). Cirrhosis, chronic obstructive lung disease, renal failure, and

Abbreviations: COX-2, cyclooxygenase 2; ECL, enterochromaffin-like; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; HP, *Helicobacter pylori*; H_2, histamine$_2$; NSAID, nonsteroidal antiinflammatory drug; PPI, proton pump inhibitor; PUD, peptic ulcer disease

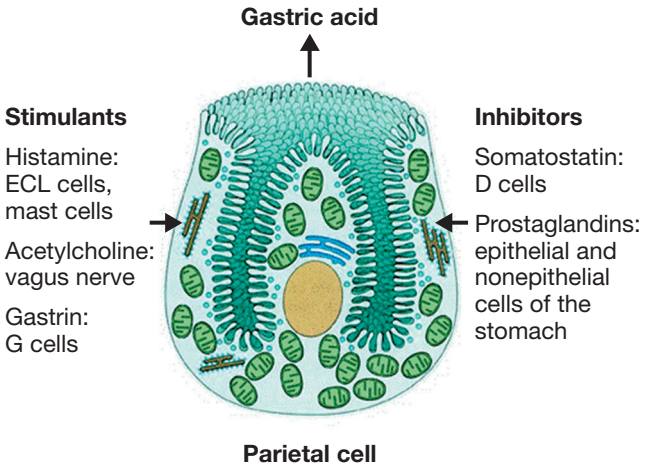

Figure 4.1. Physiology of the Parietal Cell. ECL indicates enterochromaffin-like.

organ transplant are associated with PUD, but the pathophysiologic mechanisms are unclear. When stress-related ulcerations of the stomach occur in critically ill patients, ischemia is the most likely mechanism.

HP Infection

Worldwide, HP infection is the main cause of both gastric ulcers (60%) and duodenal ulcers (up to 90%). More than half of all persons in the world are infected with HP, but only 5% to 20% of them have ulcers. In developing countries, the majority of children (>70%) are infected with HP before the age of 10 years, and more than 90% of adults by the age of 50. In the United States, HP infection is uncommon in persons born after 1945—improved sanitation and the increased use of antibiotics during childhood may be largely responsible. Persons born before 1945 are more likely to have been infected with HP (60% of them by age 60). Lower socioeconomic status, household crowding, and living with someone infected with HP are known risk factors for HP infection. In the United States, the Hispanic, African American, and elderly populations have the highest rates of HP infection. The infection rates are similar between men and women. The mode of transmission is believed to be from person to person, through oral-oral and fecal-oral routes.

HP is a gram-negative, spiral-shaped microaerophilic bacterium with multiple flagella. The organisms exist as dormant coccoid forms in culture. HP survives only on gastric-type mucosa in the stomach or metaplastic gastric-type epithelium in the duodenum, esophagus (Barrett epithelium), or small bowel (Meckel diverticulum). In the stomach, HP lives within the mucous layer, surviving the acid pH of the stomach in part by its urease activity, which converts urea (ubiquitous) to ammonia, and by its motility, its ability to adhere to epithelial cells, its microaerophilic properties, and its proteases, which may digest mucus (Figure 4.3). HP does not often survive in an alkaline environment in the stomach (eg, after gastroenterostomy).

HP damages gastric-type mucosa through its production of ammonia, proteases, lipases, phospholipases, and mucinases and by its induction of a local immune response (chemotactic factors

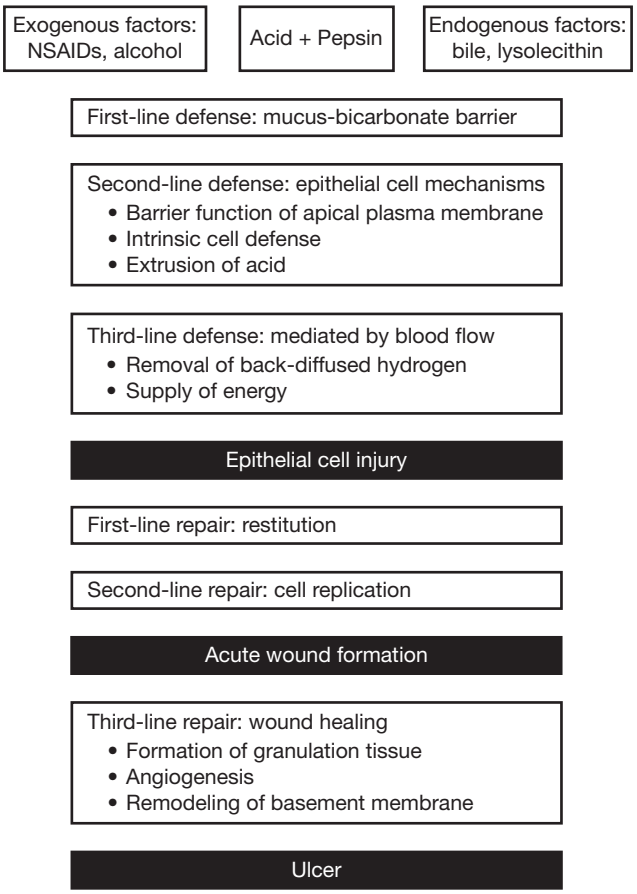

Figure 4.2. Cascade of Mucosal Defense and Repair Mechanisms. Damaging effects on epithelial cells of exogenous and endogenous factors are amplified by peptic acid activity. If the 3 lines of defense fail, epithelial cell injury occurs. Repair is by restitution and cell replication. If these repair mechanisms fail, an acute wound forms. Ulcers form only with failure of acute wound healing mechanisms. NSAID indicates nonsteroidal antiinflammatory drug. (Adapted from Soll AH. Peptic ulcer and its complications. In: Feldman M, Sleisenger MH, Scharschmidt BF, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. Vol 1. 6th ed. Philadelphia [PA]: WB Saunders Company; c1998. p. 620-78. Used with permission.)

for neutrophils and monocytes, as well as a host T-cell response). HP-specific virulence factors associated with ulcer disease include a *cag* pathogenicity island whose product (CagA) enters host epithelial cells, and certain *vacA* loci that encode a bacterial toxin (VacA). Many persons infected with HP have gastrin levels that are higher than normal because of antral-predominant active chronic gastritis that decreases the number of antral D cells and the level of somatostatin; the result is a slightly increased rate of gastric acid secretion and a greater likelihood of a duodenal ulcer developing. Higher than normal levels of gastric acid secretion may damage the duodenum and result in gastric metaplasia, allowing HP to colonize the duodenum. This pattern of duodenal ulcers appears to be more common in persons who are infected with HP later in life. In contrast, persons infected with HP early in life have a more multifocal and pangastric gastritis. These patients have parietal cell damage, decreased production of acid, and a greater likelihood of a gastric ulcer developing.

Eradication of HP eliminates gastric and duodenal ulcers and prevents recurrence. Currently, in the United States, recurrent infection with HP is less than 3% per year.

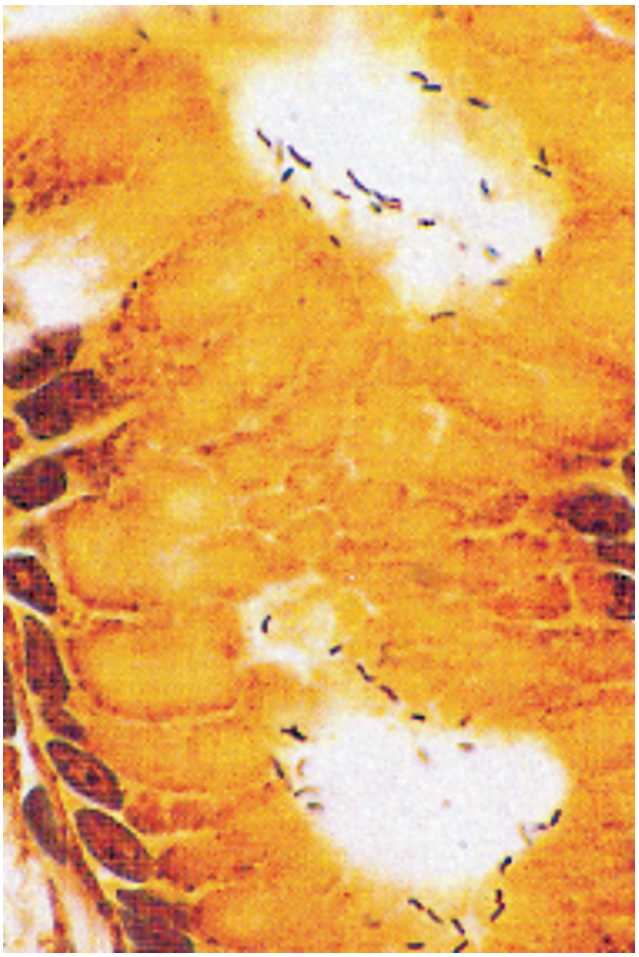

Figure 4.3. Section of Stomach Showing *Helicobacter pylori*. The bacteria are the black, rod-shaped structures (Wenger-Angritt stain). (Adapted from Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington [DC]: Armed Forces Institute of Pathology, American Registry of Pathology; c2000.)

Nonsteroidal Antiinflammatory Drugs

It is estimated that PUD develops in up to 25% of long-term users of NSAIDs and that a complication such as bleeding or perforation develops in up to 4% of them. Approximately 70% of people 65 or older use NSAIDs at least once weekly. When ingested orally, NSAIDs cause damage to the gastric epithelium topically and cause systemic damage by inhibiting the production of prostaglandins by gastroduodenal epithelial cells. Risk factors for NSAID-related gastrointestinal ulceration and its complications include age older than 60; previous history of PUD (especially if complicated); the first 30 to 90 days of NSAID therapy; use of high-dose NSAIDs or simultaneous use of multiple NSAIDs; concomitant use of corticosteroids, other antiplatelet drugs, alendronate, or anticoagulants; history of comorbid conditions; and HP infection.

The risk of injury to the gastroduodenal mucosa by aspirin is dose-related and can occur even with administration of low-dose aspirin. Because of the antiplatelet effects of aspirin and other NSAIDs, complications such as ulceration with bleeding or perforation can occur throughout the gastrointestinal tract. Cyclooxygenase 2 (COX-2) selective inhibitors have been associated with a decreased risk of clinically apparent PUD, including complications, but as with nonselective NSAIDs, there are concerns about cardiovascular risks. PUD may develop in up to 5% of patients who take COX-2 inhibitors, and ulceration in persons who continue to ingest COX-2 inhibitors may be slow to heal. COX-2 activity appears to be important for ulcer healing. Persons who take both low-dose aspirin and a COX-2 inhibitor are at increased risk for PUD and its complications compared with those who take either drug alone. Antiplatelet agents such as clopidogrel have been linked to a high rate of complications, such as gastrointestinal tract bleeding, particularly in patients who previously have had gastrointestinal tract complications, whether the antiplatelet agents were taken alone or with NSAIDs. Platelets, similar to COX-2 activity, appear to be important for ulcer healing.

HP Infection and NSAIDs

The relationship between NSAID use and HP infection is complex and controversial. Patients infected with HP with increased levels of gastric acid secretion and patients who have active or subclinical PUD are likely to be at increased risk for PUD and its complications after initiation of NSAID therapy. Two controlled trials have shown that eradication of HP infection before treatment with NSAIDs decreases these risks. In contrast, persons who take NSAIDs long-term and who have a history of complicated PUD and also are infected with HP are not protected from additional PUD complications after eradication of HP infection. Ongoing ingestion of NSAIDs perpetuates the increased risk of additional complications.

Hypersecretion of Gastric Acid

Mild hypersecretion of gastric acid occurs in many but not all patients with PUD who are infected with HP, especially in those with duodenal ulcers. Zollinger-Ellison syndrome is a rare cause of excessive hypersecretion of gastric acid. In most of these patients, ulceration of the upper gastrointestinal tract develops, often involving the esophagus, stomach, and duodenum, including ulceration of the duodenum beyond the duodenal bulb. Gastric acid hypersecretion with PUD is found in about one-third of patients who have systemic mastocytosis because of the increased release of histamine by mast cells. Increased release of histamine, acid hypersecretion, and PUD have been identified also in patients who have basophilic leukemia and chronic myelogenous leukemia with basophilia. Uncommonly, PUD patients with gastric acid hypersecretion due to hypergastrinemia who do not have Zollinger-Ellison syndrome (negative secretin test) have been found to have antral G cell hyperplasia. Many, but not all, of these patients also are infected with HP, and their PUD and gastric acid hypersecretion resolve with eradication of HP. Gastric outlet or duodenal obstruction due to various causes produces gastric distention, hypergastrinemia, hypersecretion of acid, and ulceration proximal to the obstruction. Severe PUD, hypersecretion of gastric acid, and hypergastrinemia are common in the few patients who have retained antrum syndrome after a Billroth II operation, when a small cuff of gastric antrum is left as part of the afferent limb (Figure 4.4). Finally, in patients who undergo substantial small-bowel resection, postoperative complications can include hypergastrinemia, hypersecretion of gastric acid, and severe PUD because of the sudden loss of inhibitors of gastrin and acid secretion.

Miscellaneous Conditions

Ulceration of the gastroduodenal area rarely occurs with infections other than HP. In immunocompromised patients, cytomegalovirus infection is a not uncommon cause of ulceration, often

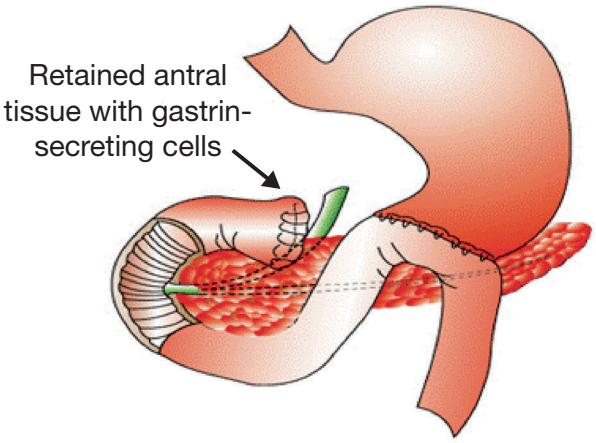

Figure 4.4. Retained Antrum After Billroth II Operation. (Adapted from Costamagna G, Loperfido S. ERCP after Billroth II reconstruction [Internet]. In: Howell DA, editor. UpToDate: Waltham [MA]. c2013. [updated 2013 Jul 20; cited 2013 Jun 11]. Available from: http://www.uptodate.com/. Used with permission.)

producing large, deep, and multiple ulcers that are frequently complicated by bleeding, perforation, or obstruction. Rarely, ulceration can occur from infections such as syphilis or tuberculosis (often antral), after radiotherapy, and from sarcoidosis, Crohn disease, vasculitis, and ischemia. Gastric ulceration can be due to malignancy, including adenocarcinoma, lymphoma, sarcoma, gastrointestinal stromal tumors, and metastatic malignancies.

Among persons who smoke cigarettes, compared with nonsmokers, PUD is more common and is more likely to be complicated, to require surgery, to be slow to heal, and to recur. Although alcohol can directly damage the gastroduodenal mucosa and stimulate acid secretion, there is no evidence that alcohol is a risk factor for PUD. Similarly, there is no clear link between either diet or psychologic factors and ulcer disease.

Clinical Features

Patients with PUD present in various ways to their medical provider. Many patients present with dyspeptic symptoms, but some are asymptomatic and others present with perforation. Ulcer-like dyspepsia is one of the most common symptoms. Classically, patients with duodenal ulcers present with epigastric burning or a hungerlike sensation, especially 1 to 3 hours after a meal or during the night. The pain improves after the ingestion of food, antacids, or antisecretory agents. Thus, these patients tend to gain weight. In contrast, persons with gastric ulcers are more likely to experience discomfort after eating and may have weight loss. Patients who have nonulcer dyspepsia can have the same symptoms as those with PUD, and many persons with PUD have atypical symptoms. Also, the overlap of symptoms between patients with gastroesophageal reflux disease (GERD) and those with PUD is considerable. The differential diagnosis for PUD includes functional dyspepsia, GERD, biliary pain, gastric or duodenal malignancy, medication side effect, pancreatitis, and ischemia.

Diagnosis

Diagnosis of PUD is difficult from the history and physical examination alone given the wide variation in presentation. The diagnosis is usually based on the results of an esophagogastroduodenoscopy (EGD) or upper gastrointestinal tract radiographic study. EGD is the preferred method of evaluation since it is more sensitive in detecting small ulcerations and can best determine the location and severity of the ulceration. In addition, biopsies can be obtained to assess for the cause of PUD, or endoscopic therapy can be applied if the ulcer is bleeding.

Table 4.1. Diagnostic Tests for *Helicobacter pylori*

Test	*Sensitivity, %*	*Specificity, %*
Nonendoscopic tests		
In-office antibody test	88-94	74-88
ELISA on serum	86-94	78-95
Stool antigen test	94	92
Urea breath test	90-96	88-98
Endoscopic tests		
Biopsy urease test	88-95	95-100
Histology	93-96	98-99
Culture	80-98	100

Abbreviation: ELISA, enzyme-linked immunosorbent assay.

Diagnosis of HP Infection

Many tests are available for diagnosing HP infection (Table 4.1). It is important to order testing only if the patient will be offered treatment for positive results. No single test is considered the criterion standard for the diagnosis of HP. Testing is divided into 2 categories, noninvasive and invasive (or endoscopic). The decision as to which test to order should be based on the clinical circumstances, pretest probability, cost, and availability of the test. In patients with PUD but no obvious cause, a second test for HP should be conducted because false-negative results are possible. Many tests (culture, histology, breath and stool antigen tests, and urease testing) depend on the number of organisms, and false-negative results are frequent if the patient has been exposed recently to antibiotics, bismuth, or a proton pump inhibitor (PPI). Patients should not receive treatment with antibiotics and bismuth for 4 to 6 weeks or with PPIs for 2 weeks (histamine$_2$ [H_2]-receptor blockers can be taken) before testing.

Serology

Serologic tests for antibodies against HP are rapid, simple, and inexpensive. Serum-based tests are more accurate than whole-blood tests. Tests that measure antibody levels in saliva are less reliable. Serologic testing is as good as any other test for the initial diagnosis of HP infection in untested or untreated persons. However, because antibody levels may remain positive indefinitely in some patients after successful treatment, serologic testing is not useful after treatment. Office-based serologic testing is less sensitive and specific than laboratory-based testing.

Stool Antigen

The HP stool antigen test is rapid, highly sensitive and highly specific but relatively expensive. In contrast to serologic testing, it can be used to evaluate active infection as well as response to therapy; thus, it is cost-effective.

Urea Breath Test

Because HP is practically the only infectious organism in the upper gastrointestinal tract capable of producing urea via urease,

urea labeled with carbon 13 or carbon 14 can be administered as a breath test. The urea breath test is rapid, highly sensitive, and highly specific but expensive. Like stool antigen testing, it is highly reliable after treatment to confirm eradication of HP.

Rapid Urease Tests

Biopsy specimens obtained during endoscopy can be tested for urease with rapid urease testing. These tests are rapid, highly sensitive, highly specific, and inexpensive. Small intestinal bacterial overgrowth can produce false-positive results (urease-producing *Proteus*), as can non-HP *Helicobacter* species. Gastrointestinal tract bleeding can cause false-negative results.

Histology

Histologic examination is highly sensitive and highly specific but expensive. Biopsy specimens (5 or 6) should be taken from the antrum, fundus, and incisura. Silver staining is recommended to facilitate the detection of HP.

Culture

HP culture after endoscopic biopsy is not widely available, is not rapid, and is less sensitive than noninvasive tests and histologic examination. It may be used best for patients with resistant HP infections to determine the antimicrobial sensitivity.

Treatment

With improved understanding of the pathogenesis of PUD, appropriate treatment has been developed. PPIs are a mainstay of therapy and are critical to ulcer healing independently of the cause. PPI therapy is superior to antacids, H_2-receptor antagonists, sucralfate, and prostaglandins. Additional treatment depends on the cause of the ulcer.

Treatment of HP Infection

Patients who test positive for HP should be given therapy to eradicate it since HP is classified as a carcinogen. Therapy is also indicated for HP-infected patients with extranodal marginal zone B-cell lymphoma or gastric adenocarcinoma. In addition, first-degree relatives of HP-infected patients with gastric adenocarcinoma should receive treatment.

The optimal therapeutic regimen for HP has not yet been defined, but the guidelines for first-line therapy for eradication of HP require 10 to 14 days of triple therapy or quadruple therapy. Triple therapy includes a PPI in combination with 2 antibiotics, preferably clarithromycin and amoxicillin (metronidazole is used instead of amoxicillin for patients allergic to penicillin) (Table 4.2). In areas where clarithromycin resistance is high (>15%-20%), the effectiveness of this triple combination therapy is less than 70%. In these areas, metronidazole should be given instead of clarithromycin. Although metronidazole resistance is not uncommon, giving metronidazole in combination with other agents (PPI, bismuth, or tetracycline) besides clarithromycin and prescribing a higher dose (500 mg twice daily) can diminish the rate of treatment failure. This first treatment course offers the highest yield of HP eradication; thus, it is important to know the resistance patterns. Resistance to amoxicillin, tetracycline, or bismuth, is rare.

Quadruple therapy can be used for first-line therapy, but it is more often reserved for patients in whom first-line therapy has failed. Quadruple therapy includes PPI, bismuth, metronidazole, and tetracycline.

If 2 regimens of therapy have failed, assess for medication nonadherence and reinforce the importance of completing the regimen. Third-line therapy can be designed on the basis of results of antibiotic sensitivity testing after culture of gastric biopsy specimens, if available. Alternatively, the combination of PPI, amoxicillin, and levofloxacin (or furazolidone) given twice daily for 14 days has been successful. After treatment, eradication of HP should be confirmed.

Treatment of NSAID Ulcers

If possible, patients should stop taking all NSAIDs in the presence of active ulceration, especially if the patient is losing blood. If NSAID therapy cannot be discontinued, dose reduction of the NSAID should be considered. In addition, PPI therapy should be started and the patient should be monitored.

Antacids

Antacids can heal ulcers by binding bile, inhibiting pepsin, and promoting angiogenesis. However, ulcer healing requires high doses of antacids, which often lead to adverse side effects. Thus, antacids are rarely used to treat PUD.

H_2-Receptor Antagonists

Four H_2-receptor antagonists (cimetidine, ranitidine, nizatidine, and famotidine) are available. All of them are highly effective for

Table 4.2. American College of Gastroenterology First-Line Regimens for *Helicobacter pylori* Eradication

Patients	*Regimen*	*Eradication Rate, %*
Patients who are *not* allergic to penicillin and have *not* previously received a macrolide	Standard-dose PPI twice daily (or esomeprazole once daily), clarithromycin 500 mg twice daily, and amoxicillin 1,000 mg twice daily for 10-14 d	70-85
Patients who *are* allergic to penicillin and who have *not* previously received a macrolide or are unable to tolerate bismuth quadruple therapy	Standard-dose PPI twice daily, clarithromycin 500 mg twice daily, and metronidazole 500 mg twice daily for 10-14 d	70-85
Patients who *are* allergic to penicillin and who *have* previously received a macrolide	Bismuth subsalicylate 525 mg orally 4 times daily, metronidazole 250 mg orally 4 times daily, tetracycline 500 mg orally 4 times daily, and ranitidine 150 mg orally twice daily (or standard-dose PPI once or twice daily) for 10-14 d	75-90

Abbreviation: PPI, proton pump inhibitor.
Adapted from Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. Am J Gastroenterol. 2007 Aug;102(8):1808-25. Epub 2007 Jun 29. Used with permission.

the treatment of PUD. Cimetidine rarely is prescribed because of its short half-life, several drug-drug interactions, and adverse effects. Cimetidine binds to cytochrome P450 and may affect the metabolism of certain drugs such as warfarin, lidocaine, theophylline, and phenytoin. It also has dose-dependent adverse effects that include gynecomastia, breast tenderness, and impotence. Ranitidine and nizatidine are longer acting, and famotidine has the longest duration of action. Healing of ulceration can be accomplished with an 8-week regimen of single bedtime dosing with any H_2 blocker. H_2-receptor blockers do not have anti-HP activity.

Proton Pump Inhibitors

PPIs are the most potent antisecretory agents available. They are enteric coated or combined with sodium bicarbonate to protect them from acid inactivation. After being absorbed in the upper small bowel, PPIs are taken up by parietal cells and secreted into the canalicular (luminal) space, where they are converted to a metabolite that binds covalently with proton pumps and irreversibly inactivates them. These proton pumps must be active, and the parietal cells must be stimulated for the PPI–proton pump interaction to occur. Thus, PPIs should be taken 15 to 30 minutes before a meal. They are not as effective if administered while acid secretion is being inhibited by H_2-receptor blockers. Several PPIs are available, including omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole. All PPIs are capable of healing duodenal ulcers in 4 weeks. Gastric ulcers, depending on size, may require a considerably longer duration of treatment.

Follow-up and Maintenance Therapy

Patients who have uncomplicated duodenal ulcers without HP infection do not require follow-up endoscopy after therapy if they do not have recurrent or persistent symptoms. Generally, follow-up endoscopy is recommended for all patients with gastric ulcers to exclude malignancy. However, about 95% of gastric cancers associated with gastric ulceration can be diagnosed at initial endoscopy when an adequate number of biopsy specimens are obtained from the edge of the ulcer (≥4) and from the base (≥1). Patients at high risk for gastric cancer or gastric ulcers with worrisome features at endoscopy should have follow-up endoscopy to document complete healing of the ulcer.

Persons with gastric or duodenal ulcers without obvious cause may benefit from maintenance PPI therapy to prevent ulcer relapse. Similarly, any patients with ulcers greater than 2 cm in diameter or ulcers complicated by fibrosis or hemorrhage may benefit from prolonged antisecretory therapy.

Prevention of PUD

Persons about to be prescribed aspirin or NSAIDs for long-term therapy should be tested for HP and treated if infected. If they are at high risk for PUD, prophylactic therapy with misoprostol or a PPI should be considered. H_2-receptor blockers have not been useful for these patients. Patients at highest risk are those with a previous history of ulcer disease; the elderly; patients also receiving treatment with warfarin, corticosteroids, or other antiplatelet agents; and those with clinically important comorbid conditions.

PUD in Pregnancy

PUD occurs uncommonly in pregnant patients. The focus of treatment during pregnancy is acid suppression. Medications that are considered safe include sucralfate and antacids, particularly the magnesium-containing antacids in the second and early third trimesters and aluminum-containing antacids in the second and third trimesters. H_2-receptor antagonists can be given since they are considered relatively safe, and PPI therapy is also considered to be low risk in pregnancy. Misoprostol is contraindicated and should be avoided because it increases the risk of major birth defects, and can cause uterine contractions and abortion. For patients with severe symptoms or symptoms refractory to treatment, an EGD can be considered to confirm the diagnosis. There should be clear communication between the obstetrician, gastroenterologist, and patient about the benefits and risks of the procedure. If HP is present, treatment is typically delayed until after delivery.

Suggested Reading

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5

Gastritis and Gastropathy

STEPHANIE L. HANSEL, MD, MS

Inflammation of the stomach can manifest itself as gastritis or gastropathy. *Gastritis* is a histologic diagnosis referring to inflammatory processes of the stomach. Gastritis may or may not have identifiable endoscopic findings or clinical symptoms. In comparison, *gastropathy* refers to epithelial damage with little or no inflammation.

There are several classifications of gastritis and gastropathy. Most of them distinguish between acute and chronic disease and the predominant inflammatory infiltrate seen in biopsy specimens. The etiology of the gastritis or gastropathy is also an important factor in the classification, as is the topography or specific areas of involvement in the stomach. The Sydney System (Table 5.1) often is used to classify chronic gastritis. It requires a total of 6 biopsies, 2 biopsy specimens each from the antrum, the body, and the incisura (Figure 5.1). In some cases, duodenal biopsies may assist in the overall diagnosis of a disease, for example, celiac disease in patients with lymphocytic gastritis, Crohn disease in patients with granulomatous gastritis, and eosinophilic gastroenteritis in patients with eosinophilic infiltration of the antrum.

Gastritis

Acute Gastritis

By definition, *acute gastritis* is an acute inflammatory process that involves the stomach with a predominantly neutrophilic infiltration. It may or may not have features of intramucosal hemorrhage, superficial mucosal sloughing, or erosion. Most often, acute gastritis is related to aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), excess alcohol intake, uremic toxins, heavy tobacco use, cancer chemotherapeutic drugs, ischemia, or infection.

Acute gastritis due to *Helicobacter pylori* (HP) infection is rarely identified. Abdominal pain, nausea, or vomiting may develop. Endoscopic findings such as erythema or erosion are absent or nonspecific. Biopsy specimens show mucosal neutrophilic infiltration in the antrum, with or without desquamation and erosions. In the great majority of persons acutely infected with HP, an active chronic gastritis develops.

Aspirin and NSAIDs can produce an acute injury to the gastric mucosa. With gastritis, endoscopic findings range from minimally visible changes to erythema, petechial hemorrhages, or erosions. Histologically, there can be evidence of superficial lamina propria hemorrhage, mucosal sloughing, neutrophilic infiltration, and mucosal necrosis. The changes are limited to the mucosa and do not extend into the muscularis mucosa. Clinical symptoms such as abdominal pain, nausea, vomiting, or gastrointestinal tract bleeding may or may not be present as well. Similar findings occur after the ingestion of large amounts of alcohol and other toxic substances and after ischemia (Figure 5.2). All these insults impair mucosal barrier function by affecting prostaglandin synthesis (NSAIDs) or mucosal blood flow (alcohol or ischemia) or by direct injury to the surface mucosal cells (NSAIDs, other drugs, or infection). Treatment of acute gastritis includes management of the underlying condition, withdrawal of any offending drug or toxin, and acid-suppression therapy with a proton pump inhibitor.

Chronic Gastritis

Chronic gastritis is classified in the Sydney System as nonatrophic, atrophic, or special forms. Mucosal injury occurs in all forms of chronic gastritis. The atrophic forms of chronic gastritis

Abbreviations: CMV, cytomegalovirus; HP, *Helicobacter pylori*; NSAID, nonsteroidal antiinflammatory drug

Table 5.1. Sydney System for Classification of Chronic Gastritis

Type of Gastritis	*Etiologic Factors*	*Gastritis Synonyms*
Nonatrophic	*Helicobacter pylori*	Superficial
		Diffuse antral gastritis
		Chronic antral gastritis
		Interstitial follicular
		Type B
Atrophic-autoimmune	Autoimmunity	Type A
	H pylori	Diffuse corporeal
		Pernicious anemia
Atrophic-multifocal	*H pylori*	Type B
		Environmental
		Metaplastic
		Atrophic pangastritis
		Progressive intestinalizing pangastritis
Chemical/radiation	Bile	Reactive
	Nonsteroidal antiinflammatory drugs	Reflux
	Alcohol or other agents (possibly)	Radiation
	Radiation	
Lymphocytic	Idiopathic	Varioliform
	Autoimmune	Celiac-associated
	Gluten	
	H pylori	
Granulomatous	Crohn disease	Isolated granulomatous
	Sarcoidosis	
	Wegener granulomatosis	
	Infectious	
Eosinophilic	Food sensitivities	Allergic
	Allergies	
	Idiopathic	
Infectious gastritides	Bacteria	Phlegmonous
	Viruses	Cytomegalovirus
	Fungi	Anisakiasis
	Parasites	

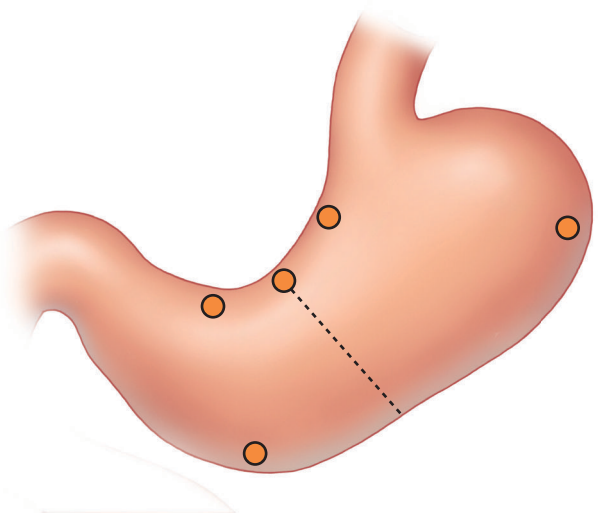

Figure 5.1. Gastric Biopsy Protocol to Diagnose Gastritis. Biopsy specimens (circles) should be obtained from the greater and lesser curvatures of the body and the antrum and from the incisura (dotted line).

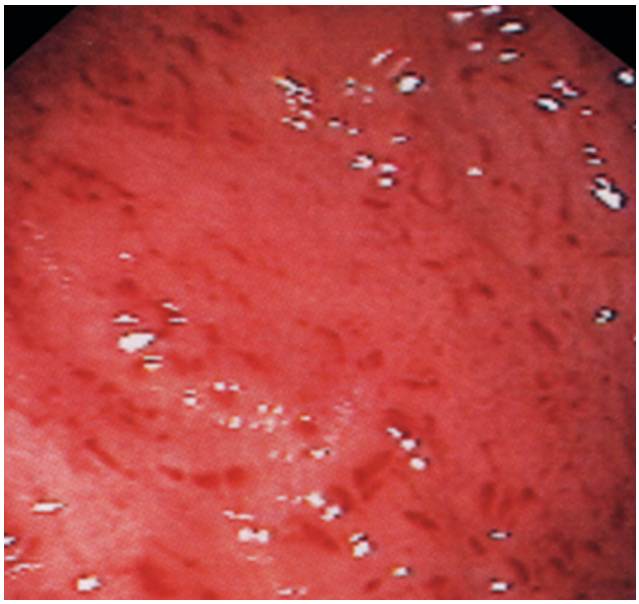

Figure 5.2. Acute Hemorrhagic Gastritis. (From Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; c2000. p. 101.)

can be autoimmune or multifocal, and, subsequently, metaplasia, dysplasia, and carcinoma may develop.

Nonatrophic Chronic Gastritis

Nonatrophic chronic gastritis is typical in HP-infected persons with acute gastritis who do not clear the infection (Figure 5.3). Endoscopically, gastric mucosal erythema, erosions, granularity, and nodularity may be seen. It usually is most evident in the antrum. Histologically, there is marked lymphoplasmacytic and neutrophilic infiltrate. Lymphoid aggregates or germinal centers may be seen. Gastric atrophy, metaplasia, and dysplasia are not seen. However, this type of active chronic gastritis due to HP infection does increase the risk of duodenal ulcer disease.

Atrophic Chronic Gastritis

Multifocal Atrophic Gastritis. Multifocal atrophic gastritis may develop in persons infected with HP. This type of active chronic gastritis includes the loss of glands and metaplastic change principally involving the body and antrum of the stomach (Figure 5.4). Inflammation consists of both acute and chronic inflammatory cells. There is an increased risk of gastric ulcer disease and gastric adenocarcinoma with this type of gastritis.

Autoimmune Atrophic Gastritis. Patients with autoimmune atrophic gastritis can present with abdominal discomfort or pain, weight loss, and pernicious anemia. This type of gastritis is an autosomal dominant condition and is responsible for less than 5% of all cases of chronic gastritis (Figure 5.5). It involves the body and fundus of the stomach, sparing the antrum. Endoscopically, there is a loss of gastric folds and prominence of the submucosal vasculature. Laboratory findings include autoantibodies to parietal cells and intrinsic factor, elevated serum gastrin level, and low vitamin B_{12} level. Hypochlorhydria, achlorhydria, iron deficiency, or pernicious anemia may develop in some but not all patients. Histologically, the abnormal findings are limited to the body and fundic mucosa. Typically, there is a loss of oxyntic glands (chief and parietal cells) and a prominent lamina propria lymphocytic and plasma cell infiltration directed at the fundic glands. Patients do have a small risk of gastric carcinoids (<10%) and gastric carcinoma (<3%). Patients or their relatives may have other autoimmune disorders, including Hashimoto thyroiditis, Graves disease, Addison disease, diabetes mellitus, and vitiligo. There is also an association with HLA-B8 and HLA-DR3.

Special Forms of Gastritis

Infectious Gastritis. Bacterial gastritis is most often caused by HP (see Chapter 4, "Peptic Ulcer Disease"). However, other species of bacteria may be found in the stomach after antrectomy or in association with achlorhydria. Organisms such as *Streptococcus, Staphylococcus, Lactobacillus, Bacteroides, Klebsiella,* and *Escherichia coli* have all been cultured from gastric juice but rarely are of clinical significance. These organisms likely represent oral flora that has been swallowed. In circumstances of

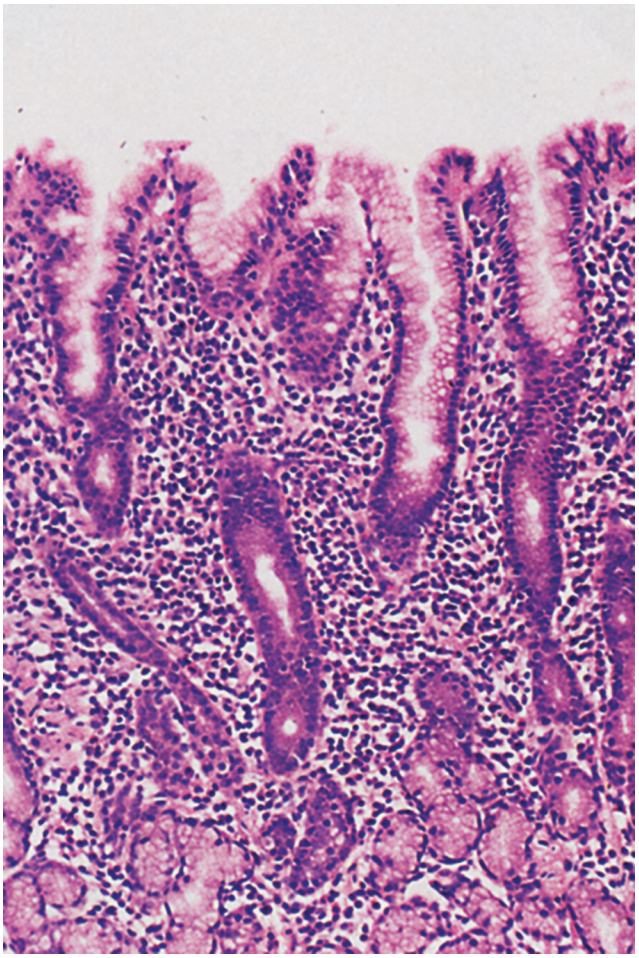

Figure 5.3. Active (Nonatrophic) Chronic Gastritis of the Antrum of the Stomach. Stain is hematoxylin-eosin. (From Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; c2000. p. 90.)

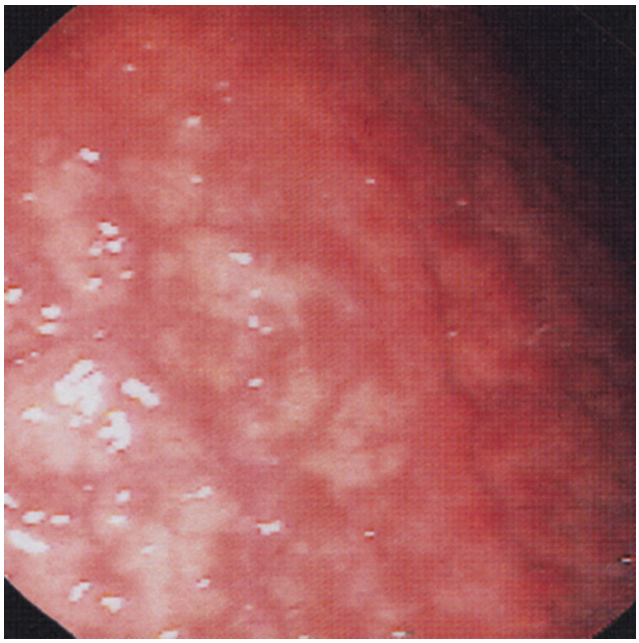

Figure 5.4. Multifocal Atrophic Gastritis. (From Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; c2000. p. 93.)

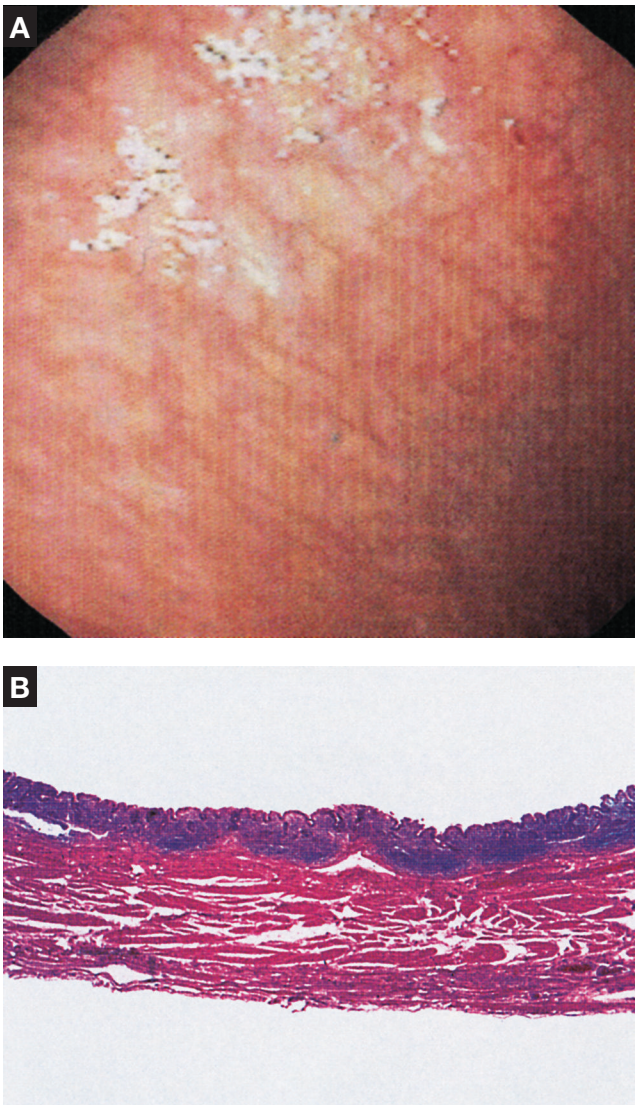

Figure 5.5. Chronic Autoimmune Atrophic Gastritis. A, Gross appearance. B, Section through the body of the stomach (hematoxylin-eosin stain). (From Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; c2000. p. 94.)

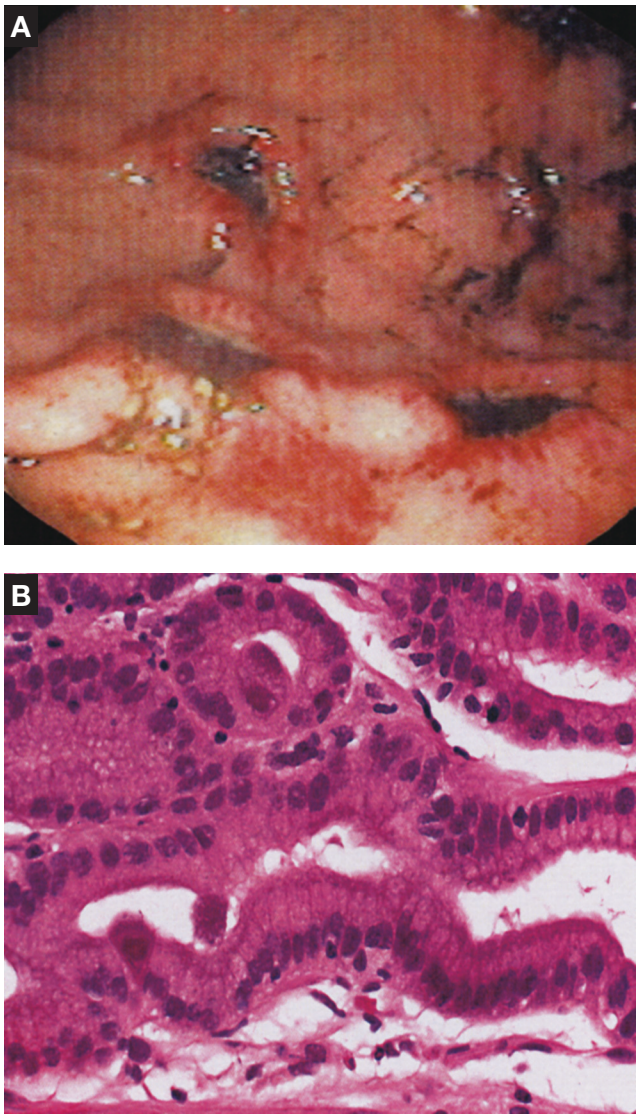

Figure 5.6. Cytomegalovirus (CMV) Infection of the Stomach. A, Gross appearance of CMV ulcers. B, CMV gastropathy (hematoxylin-eosin stain). (From Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; c2000. p. 123.)

ischemia or immunosuppression, these organisms may produce marked morbidity.

Mycobacterium tuberculosis is an important cause of bacterial gastritis in developing countries. Patients present with weight loss, anorexia, night sweats, and fevers and can have symptoms of gastric outlet obstruction. Biopsies from ulcerated or nodular areas with stains for acid-fast bacilli and tuberculosis cultures are necessary for diagnosis. Secondary or tertiary syphilis can also involve the stomach, especially the antrum.

Phlegmonous gastritis is a rare, life-threatening condition associated with full-thickness purulent necrosis of the gastric wall. Multiple bacteria are responsible, and it usually occurs in immunocompromised patients, including alcoholics and patients with diabetes mellitus. Invasive procedures may trigger the onset, with fever, chills, abdominal pain, and hypotension being common. If gas-forming organisms are involved, emphysematous changes may be apparent on imaging studies. The mortality rate is high, and surgery may be required to remove the necrotic portion of the stomach.

Cytomegalovirus (CMV) infection is the most commonly recognized viral infection of the stomach (Figure 5.6). This infection may or may not have endoscopic findings that include edema, erythema, erosions, or ulcers. Patients with CMV infection of the stomach may or may not have symptoms, such as fever, abdominal pain, nausea, vomiting, or bleeding, and they usually are immunosuppressed. Biopsy specimens from macroscopically involved and apparently normal areas may show typical cytomegalic cells and inclusions. When ulceration is present, biopsy specimens from the center of the ulcer are more likely to be diagnostic than specimens from the edge because of vascular endothelial involvement of this virus. In cases in which the diagnosis is in doubt, immunohistochemistry enhances the diagnostic yield.

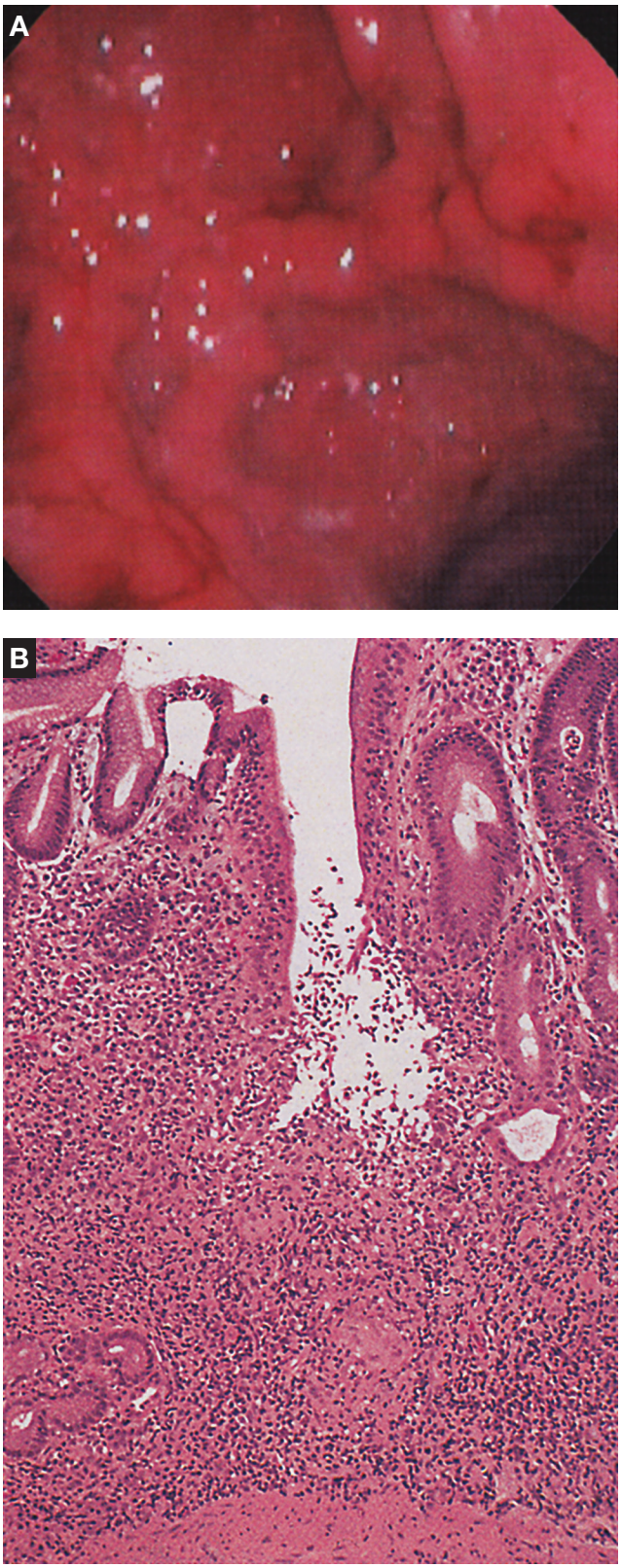

Figure 5.7. Granulomatous Gastritis. A, Gross appearance. B, Histologic appearance of granuloma (hematoxylin-eosin stain). (From Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; c2000. p. 98, 99.)

Fungal and parasitic infections of the stomach are uncommon. In immunosuppressed patients, gastric infections may be caused by *Histoplasma, Candida, Aspergillus, Cryptococcus, Torulopsis*, or mucormycosis. Ingestion of raw fish can result in anisakiasis. *Cryptosporidium* and *Strongyloides* infections do not commonly involve the stomach, especially in immunosuppressed patients.

Noninfectious Granulomatous Gastritis. In the absence of infection, granulomatous gastritis (Figure 5.7) occurs most commonly with Crohn disease (52%). The differential diagnosis includes isolated granulomatous gastritis (25%), foreign body granuloma (10%; eg, suture, food), tumor-associated granuloma, sarcoidosis, infection (HP, tuberculosis, histoplasmosis, syphilis), and vasculitis-associated granulomas. Most often, an antral inflammatory infiltration is found. Many patients with granulomatous gastritis are asymptomatic. In a few patients, particularly those with Crohn disease or sarcoidosis, symptoms of gastric outlet obstruction due to ulceration and scarring of the antrum and pylorus can develop. Nonspecific treatment, such as acid-reduction therapy, or therapy directed toward the underlying disorder usually is indicated.

Lymphocytic Gastritis. Lymphocytic gastritis is uncommon and often is asymptomatic. If symptoms do occur, dyspepsia and diarrhea are the most common. On endoscopy, mucosal nodules, erosions, and enlarged gastric folds may be seen. Histologically, there is active chronic pangastritis with epithelial infiltration by mature lymphocytes, usually T lymphocytes (Figure 5.8). The lamina propria is expanded by the lymphocytes and plasma cells. Most often, when found in patients with celiac disease, lymphocytic gastritis is antral predominant. However, when lymphocytic gastritis occurs in patients with HP infection, it tends to be gastric body predominant and often has polymorphonuclear cells. Staining for HP should be performed in every case of lymphocytic gastritis. Patients with microscopic colitis or Ménétrier disease may also have lymphocytic gastritis. Therapy is directed toward the underlying condition.

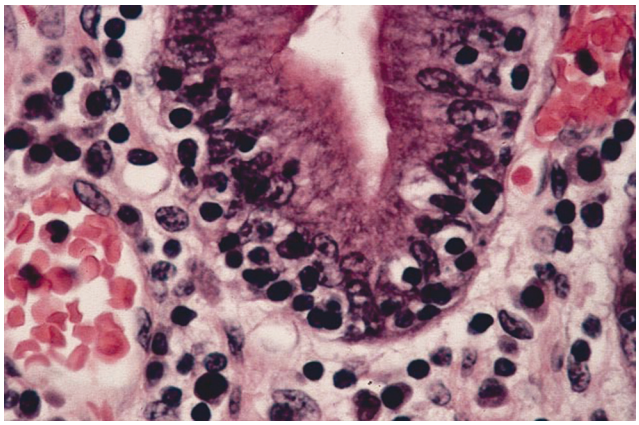

Figure 5.8. Lymphocytic Gastritis. Intraepithelial lymphocytes can be seen without any destruction of surrounding epithelial cells (hematoxylin-eosin stain). (From Owen DA. Gastritis and carditis. Mod Pathol. 2003 Apr;16[4]:325-41. Used with permission.)

Eosinophilic Gastritis. A wide variety of disorders are associated with eosinophilic infiltration of the stomach, including parasitic infestation, hypereosinophilic syndrome, gastric Crohn disease, gastric carcinoma, lymphoma, connective tissue disorder, peptic ulcer disease, mast cell disease, and Churg-Strauss vasculitis. Eosinophilic gastroenteritis, also called allergic gastroenteritis, is a rare inflammatory condition. Patients generally have a history of allergy, asthma, food intolerance, eczema, drug sensitivities, or peripheral eosinophilia and increased serum levels of immunoglobulin E. On endoscopy, the gastric mucosa ranges from normal to erosions and erythema. In the most common mucosa-predominant form, biopsy specimens typically show patchy but dense eosinophilic infiltration (Figure 5.9). The antrum is typically involved. Less commonly, full-thickness or open biopsy may be necessary for diagnosis if only the muscle or serosa layers are affected. Corticosteroids are used for treatment.

Gastropathy

Chemical Gastropathy

Long-term exposure to substances that can damage the gastric mucosa can result in chronic gastropathy. Other common names for this condition include reactive gastritis, reactive gastropathy, and bile reflux gastritis or gastropathy. The etiology includes aspirin or NSAIDs, bile reflux, and alcohol. Endoscopic findings include edema, erythema, erosions, and visible bile in the stomach. The antrum is most commonly involved, and biopsy specimens show foveolar hyperplasia, loss of mucin, proliferation of lamina propria smooth muscle, and vascular congestion in the lamina propria. Bile reflux gastropathy usually follows surgical intervention, such as gastroenterostomy, vagotomy, or pyloroplasty, but can occur in persons with gastric emptying disorders or in stomachs that have not had a surgical procedure. Symptoms such as epigastric discomfort, nausea, and vomiting do not correlate well with endoscopic or histologic findings. Treatment of chemical gastropathy includes discontinuing use of the offending agent if possible and using acid-reducing medication and ursodiol if bile acid is the most likely cause. Cholestyramine, sucralfate, and aluminum-containing antacids have been prescribed for bile acid gastropathy but have mostly been unsuccessful. Ursodiol has been shown to decrease symptoms without improving histologic findings. A surgical Roux-en-Y revision to divert bile from the stomach in patients with previous gastroenterostomy and symptomatic bile reflux gastropathy has been found to reduce symptoms in 50% to 90% of these patients.

Vascular Gastropathies

Vascular gastropathies are defined as abnormalities of the gastric vasculature affecting mucosal blood vessels, with little or no inflammation. Typical examples include congestive gastropathy from congestive heart failure, portal hypertensive gastropathy, and gastric vascular ectasia (ie, watermelon stomach).

In patients with portal hypertension, dilatation and sclerosis of small mucosal and submucosal venules and capillaries can produce an endoscopically recognizable mucosal mosaic pattern, usually most prominent in the fundus and body of the stomach (Figure 5.10). Nodularity and punctate erythema also may be seen. Clinically, patients may have iron deficiency anemia or melena. Treatment involves attempts to lower portal pressure; endoscopic therapy is not effective (see Chapter 26, "Vascular Diseases of the Liver").

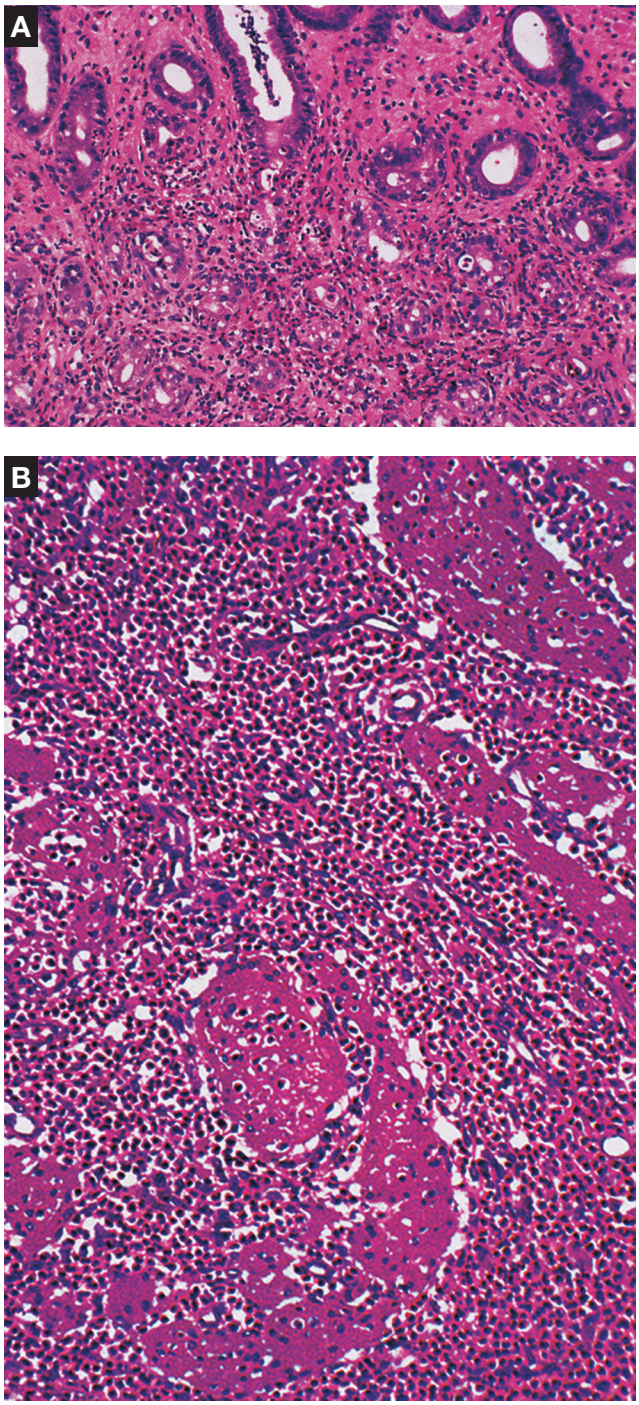

Figure 5.9. Eosinophilic Gastritis. Note the marked eosinophilic infiltration. A, High-power view. B, Low-power view. (From Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; c2000. p. 97.)

Patients with gastric vascular ectasia develop dilated mucosal capillaries with fibrin thrombi and fibromuscular hyperplasia of the lamina propria with minimal or no inflammation. Endoscopic findings typically include linear or nodular erythematous streaks without a mosaic pattern, usually involving the antrum but sometimes extending into the gastric body (Figure 5.11). Gastric vascular ectasia tends to occur in patients who have an array of underlying conditions, including pernicious anemia, collagen

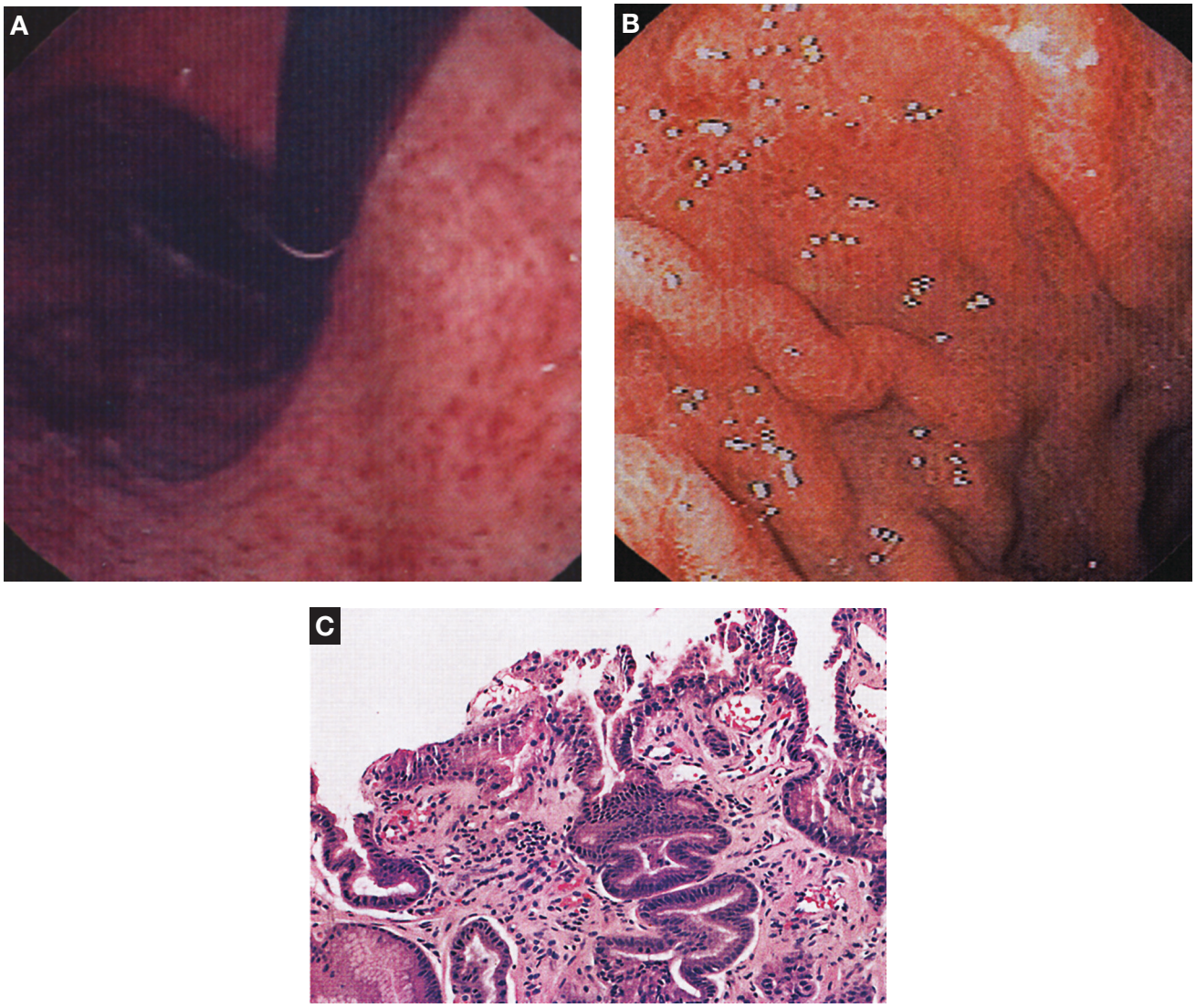

Figure 5.10. Portal Hypertensive Gastropathy. A and B, Gross specimens showing the mosaic mucosal pattern. C, Histologic section showing dilated, tortuous blood vessels (hematoxylin-eosin stain). (From Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; c2000. p. 116.)

vascular disease, cirrhosis, renal failure, bone marrow transplant, and antral mucosal trauma (as in pyloric prolapse). Similar to patients with portal hypertensive gastropathy, patients may have iron deficiency anemia or melena. Endoscopic therapy with argon plasma coagulation can diminish blood loss in patients with anemia (see Chapter 11, "Nonvariceal Gastrointestinal Tract Bleeding"). Of note, liver transplant can benefit patients with gastric vascular ectasia who have cirrhosis, but transjugular intrahepatic portosystemic shunts are not helpful (see Chapter 26, "Vascular Diseases of the Liver").

Hypertrophic Gastropathy

Hypertrophic gastropathy refers to a group of conditions with giant enlargement of the rugal folds. This group includes some cases of chronic gastritis from HP infection or lymphocytic gastritis, Zollinger-Ellison syndrome, infiltrative disorders (sarcoidosis and malignancy), and Ménétrier disease. Patients with Ménétrier disease often have such symptoms as epigastric pain, nausea, vomiting, diarrhea, edema, and weight loss. Many patients have evidence of a protein-losing enteropathy manifested by low serum level of albumin and increased stool clearance of $alpha_1$-antitrypsin. Endoscopically, giant gastric rugal folds and a cobblestone pattern are present but may spare the antrum. A full-thickness gastric biopsy specimen or endoscopic snare biopsy specimen from an enlarged fold usually is necessary to make the diagnosis. Histologic examination shows extreme surface mucous cell hyperplasia with deeper glandular atrophy. Often, gastric hypochlorhydria or achlorhydria is present together with excessive secretion of mucus. Increased levels of transforming growth factor-α may be responsible for the histologic changes. Improvement in symptoms after the subcutaneous administration of octreotide has been inconsistent. In addition to gastric resection, treatment with investigational agents to counteract the effects of transforming growth factor-α has been successful. It is unclear whether patients with Ménétrier disease have an increased risk of gastric adenocarcinoma.

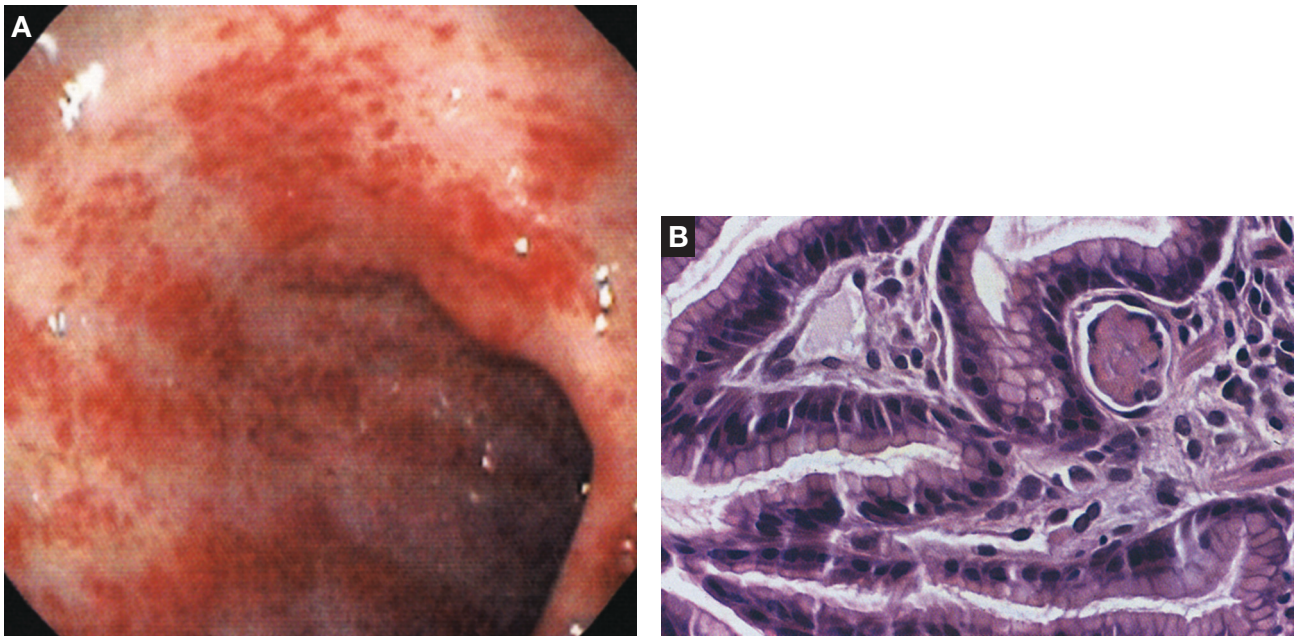

Figure 5.11. Watermelon Stomach (Antrum). A, Gross specimen. B, Histologic section showing thick-walled, ectatic vessels (hematoxylin-eosin stain). (From Emory TS, Carpenter HA, Gostout CJ, Sobin LH. Atlas of gastrointestinal endoscopy & endoscopic biopsies. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; c2000. p. 118.)

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6

Gastric Neoplasms and Gastroenteric and Pancreatic Neuroendocrine Tumors[a]

MARK V. LARSON, MD

Gastric neoplasms are an important contributor to cancer-related mortality. Of the various neoplasms that can affect the stomach, adenocarcinoma is the most common and accounts for up to 95% of all gastric neoplasms. Less common are gastric lymphomas, gastrointestinal stromal tumors (GISTs), neuroendocrine tumors (NETs), and metastatic disease involving the stomach (Table 6.1). This chapter considers the epidemiology, pathogenesis, clinical manifestation, diagnostic evaluation, treatment, and prognosis of these neoplastic diseases.

Gastric Adenocarcinoma

Epidemiology

The first statistical description of cancer incidence and mortality, from the late 1700s, showed that gastric cancer was the most common and most lethal of malignancies. Although the gastric cancer incidence and mortality have decreased since the 1930s, gastric adenocarcinoma remains the second most common cancer worldwide, with approximately 870,000 new cases and 650,000 deaths annually. Gastric cancer is rare in persons younger than 40 years, but its incidence increases steadily thereafter, peaking in the seventh decade of life.

The incidence of gastric cancer varies by geographic location, with 60% of gastric cancers occurring in the developing world. The highest incidence rates are in eastern Asia, the mountainous regions of South America, and eastern Europe. The lowest incidence rates are primarily in the industrialized nations in North America, northern Europe, and southeastern Asia. Regardless of region, gastric cancer is more common in men than in women.

In the United States, gastric cancer is diagnosed in approximately 21,000 patients annually, and over 10,000 are expected to die of gastric cancer each year. Although gastric cancer is relatively infrequent in North America, its contribution to the burden of cancer deaths is substantial: It is the third most common gastrointestinal tract malignancy, after colorectal and pancreatic cancer, and the third most lethal neoplasm overall.

The worldwide incidence of gastric cancer has decreased since the middle of the 20th century. Gastric cancer was the leading cause of cancer deaths in the world until it was surpassed by lung cancer in the 1980s. Part of the decrease in gastric cancer in the United States may be due to the recognition and alteration of certain risk factors, such as the identification and treatment of *Helicobacter pylori* infection and changes in dietary trends. The increasingly widespread use of refrigerators was likely the initial turning point for the decrease in the incidence of gastric cancer. Refrigeration decreased bacterial and fungal contamination of food, increased the availability of fresh fruits and vegetables (which provide protective antioxidants), and lessened the

[a] Portions of this chapter were adapted from Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. Ann Surg. 2005 Jan;241(1):27-39. Used with permission.

Abbreviations: CgA, chromogranin A; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; ENMZL, extranodal margin zone B-cell lymphoma; EUS, endoscopic ultrasonography 5-HIAA, 5-hydroxyindoleacetic acid; GIST, gastrointestinal stromal tumor; GNET, gastroenteric neuroendocrine tumor; MALT, mucosa-associated lymphoid tissue; MEN, multiple endocrine neoplasia; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PET, positron emission tomography; PNET, pancreatic neuroendocrine tumor; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SEER, Surveillance, Epidemiology, and End Results; SRS, somatostatin receptor scintigraphy; VIP, vasoactive intestinal polypeptide; WDHA, watery diarrhea, hypokalemia, and achlorhydria

Table 6.1. Frequency of Different Types of Gastric Neoplasms

Tumor Type	*Percentage of Gastric Neoplasms*
Adenocarcinoma	90-95
Lymphomas (diffuse large B cell and extranodal marginal zone B cell)	5
Gastroenteric and pancreatic neuroendocrine tumors (including carcinoids), gastrointestinal stromal tumors, and metastic disease to the stomach	<5

need for salt-based preservation—all of which may have reduced some of the most significant risk factors for gastric cancer. Although the incidence of gastric cancer overall is decreasing, the absolute number of new cases per year is increasing because of an increased and aging world population. Consequently, gastric cancer will continue to be an important cause of cancer and cancer-related death for the foreseeable future.

Pathogenesis

Much effort has been made to understand the etiology of gastric adenocarcinoma. It is widely held that there is no single cause but rather multiple causative factors, including diet, exogenous substances, infectious agents, and genetic factors.

Gastric adenocarcinoma has 2 separate forms: *intestinal* (or well-differentiated) and *diffuse* (or undifferentiated). They have distinct histologic appearances and molecular genetic profiles and appear to follow separate pathogenetic pathways. A key difference is the presence or absence of intercellular adhesion molecules produced when there is expression of the cell adhesion protein E-cadherin or *CDH1* gene.

In diffuse tumors, 1 of the initial carcinogenic events is the loss of expression of E-cadherin, which is critical for establishing intercellular connections and maintaining the organization of epithelial tissues. Without this protein, individual tumor cells tend to invade surrounding tissues without forming typical epithelial glands. Diffuse-type gastric cancers have a tendency to invade and then broadly extend along the gastric wall. Occasionally, the stomach is infiltrated extensively, giving it a rigid, fixed appearance, a condition known as *linitis plastica*. Diffuse-type tumors are highly metastatic and are characterized by rapid disease progression and generally a poor prognosis.

In contrast, intercellular adhesion molecules are well preserved in intestinal-type gastric adenocarcinomas, and the tumor cells tend to occur in tubular or glandular formations, similar in appearance to adenocarcinomas in the colorectum and small intestine. The pathogenesis appears to follow a multistep progression that usually results from *H pylori* infection. The first stage is chronic gastritis, during which there are fluctuating periods of greater or lesser inflammatory infiltrates. In some patients, this process results in atrophic gastritis, sometimes referred to as gastric atrophy, which is the multifocal disappearance of gastric glands within the epithelium. Multifocal atrophy may be followed by the appearance of glands that mimic intestinal epithelial glands. This represents intestinal metaplasia. The larger the atrophic and metaplastic areas, the greater the chance that dysplastic cells will develop within these areas. Dysplastic cells are precancerous. As these cells undergo increasing degrees of nuclear atypia and cellular disorganization, evolving from low-grade to high-grade dysplasia, there is a greater chance they will develop into an invasive, intestinal-type adenocarcinoma.

Intestinal-type gastric adenocarcinoma does not develop de novo. Whether the cause is autoimmune or from environmental factors or *H pylori* infection, gastritis is usually the first step in cancer induction. A sequence of pathologic changes occurs, beginning with inflammation, which is followed by intestinal metaplasia and then dysplasia as mutations accumulate in rapidly dividing inflammatory cells, and, finally, intestinal-type cancer. This model of gastric carcinogenesis is commonly referred to as the Correa Cascade, named after the gastrointestinal pathologist who first described this sequence of tissue changes leading to cancer.

Although intestinal metaplasia is clearly an intermediate step, it is difficult to quantify the significance or magnitude of the risk of progressing to gastric carcinoma after intestinal metaplasia appears. High-risk subsets include patients who have a family history of gastric cancer or who are members of high-risk ethnic populations and patients who have dysplasia on biopsies or extensive areas of the stomach with biopsy-proven intestinal metaplasia. Among patients with chronic autoimmune gastritis, it is estimated that gastric adenocarcinoma develops in 1% to 3% of patients, which is significantly higher than in an age-matched population.

Risk Factors

Diet

Epidemiologic studies have documented an association between diet and gastric cancer. Although dietary factors have been shown to influence the development of gastric cancer, specific substances have not been isolated. The most consistent association is the ingestion of nitroso compounds. Nitroso compounds are formed from nitrates, which are found naturally in foods such as vegetables and potatoes but are also used as preservatives for meats, cheeses, and pickled foods. These preservatives were common in foods before the era of refrigerators. Regions where nitrate-based fertilizers are used also have a higher incidence of gastric cancer.

Diets high in salt also have been linked with an increased incidence of gastric cancer. In animal models, high salt intake has been associated with atrophic gastritis. Diets low in uncooked fruits (particularly citrus fruits) and vegetables and high in processed meat, fried food, and alcohol are associated with an increased risk of gastric cancer. The protective effect from fruits and vegetables is thought to be from their vitamin C content, which may decrease the formation of nitroso compounds inside the stomach.

Tobacco Use

Smoking increases the risk of gastric cancer, especially in men, at least 1.5-fold. This risk decreases after 10 years of smoking cessation. Socioeconomic status also affects the risk of gastric cancer. Distal cancer is 2-fold higher among patients of low socioeconomic status, and proximal gastric cancer is more likely among those of higher socioeconomic status.

Gastric Surgery

Patients who have had gastric surgery have a higher risk of gastric cancer. This risk is greatest 15 to 20 years after the operation. Billroth II surgery carries a higher risk than Billroth I surgery, most likely because Billroth II surgery increases the reflux of bile and pancreatic juices into the stomach, which is thought to be

instrumental in the development of gastric cancer. Because this risk is low, patients who have had a partial gastric resection do not warrant endoscopic screening.

Infection

The most important risk factor for the development of gastric malignancies is *H pylori* infection of the stomach. Although persistent viral infection leads to several cancers, *H pylori* infection was the first bacterial infection linked to a human cancer. In 1994, the World Health Organization classified *H pylori* as a group 1 human carcinogen for gastric adenocarcinoma. *Helicobacter pylori* is also a key component in the pathogenesis of gastric mucosa–associated lymphoma. As reviewed above, *H pylori* infection most likely triggers inflammation that results in atrophy and may progress to intestinal metaplasia, dysplasia, and cancer. Although gastric cancer develops in few patients with *H pylori* infection, 90% of those with gastric cancer have evidence of *H pylori* infection.

The precise mechanism by which *H pylori* infection leads to gastric cancer is not understood clearly. It is well established that *H pylori* infection leads to chronic gastritis. The inflammation associated with chronic gastritis reduces the mucous layer overlying mucosal cells and exposes these cells to mutagenic compounds (eg, nitroso compounds and free radicals). Chronic infection with *H pylori* can result in the destruction of the gastric mucosa, leading to atrophic gastritis. *Helicobacter pylori* infection has been associated most strongly with cancers in the distal portion of the stomach and does not seem to be associated with cancers involving the gastroesophageal junction and cardia regions. All first-degree relatives of persons with gastric cancer should be tested for *H pylori* infection and should be treated if infected.

Genetics

Genetic predisposition to the development of gastric cancer has been identified. First-degree relatives of patients with gastric cancer have at least a 2-fold greater incidence of this cancer than the general population. Gastric cancer occasionally develops in families with germline mutations in the p53 gene (Li-Fraumeni syndrome) and *BRCA2*. In 1% of gastric cancers, germline mutations in *CDH1*, the gene encoding E-cadherin, leads to an autosomal dominant predisposition to gastric carcinoma, referred to as *hereditary diffuse gastric cancer*, which has a penetrance of approximately 70%. It has been suggested that identification of the E-cadherin mutation should prompt prophylactic gastrectomy in affected kindreds.

Certain cancer syndromes that have been associated with gastric cancer include familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, and Peutz-Jeghers syndrome.

Blood group A appears to confer an increased risk of gastric cancer. Possibly, however, the increased risk is not associated with the blood group antigens themselves but rather with the effects of the genes associated with them.

Gastric Disorders

Pernicious anemia is an autoimmune-type atrophic gastritis. Patients with this condition have an increased risk of gastric cancer. Gastric polyps also may increase the risk of gastric cancer. These polyps are usually asymptomatic and found incidentally. Most gastric polyps are hyperplastic, without malignant potential. Adenomatous polyps are less common but may give rise to or coexist with gastric adenocarcinoma. Adenomatous polyps usually occur in areas of chronic atrophic gastritis. Because of their malignant potential, they should be removed under most circumstances.

Hypertrophic gastropathy (Ménétrier disease) is a rare, idiopathic condition characterized by rugal fold hypertrophy, hypochlorhydria, and protein-losing enteropathy. Gastric cancer reportedly occurs in up to 10% of patients with this disease.

Clinical Features

Weight loss and persistent mid-epigastric pain are the most common symptoms at initial presentation, but for many patients, the symptoms are so vague that the diagnosis is delayed. Patients may complain of early satiety, abdominal bloating, meal-induced dyspepsia, nausea, or anorexia. Abdominal pain in the epigastric area may be mild and intermittent initially but more severe and constant as the disease progresses. Patients with cancer involving the distal antrum or pylorus may have persistent vomiting due to gastric outlet obstruction. Occult or overt bleeding may occur in early- or late-stage cancers. Dysphagia is a prominent symptom in lesions of the gastric cardia or gastroesophageal junction.

Patients who have a diffuse cancer called linitis plastica, characterized by poor distensibility of the stomach, may present with nausea and early satiety. Occult gastrointestinal tract bleeding with or without iron deficiency anemia is not uncommon, while overt bleeding (eg, hematemesis) is seen infrequently.

A pseudoachalasia syndrome may occur as the result of tumor involvement of the gastroesophageal junction area. For this reason, gastric malignancy must always be considered when older patients present with symptoms suggestive of achalasia.

Gastric cancer spreads by direct extension through the stomach wall to perigastric tissue, and it invades adjacent structures, including the pancreas, colon, spleen, kidney, and liver. Lymphatic metastases occur early, and local and regional nodes are the first to be involved. The disease then spreads to more distant intra-abdominal lymph nodes as well as to the supraclavicular region (Virchow node), periumbilical area (Sister Mary Joseph nodule), or left axilla (Irish node), or it may result in peritoneal carcinomatosis with malignant ascites. The liver is the most common site of hematogenous spread, followed by the lungs, bones, and brain.

Patients with gastric cancer occasionally present with paraneoplastic syndromes such as acanthosis nigricans, the sign of Leser-Trélat (sudden onset of diffuse seborrheic keratoses on the trunk), venous thromboses, or dermatomyositis.

Tumor Features

Location

Endoscopically, gastric adenocarcinoma may appear as an exophytic, polypoid mass or as an irregular, infiltrating lesion with surface nodularity or ulceration. The location of the primary tumor in the stomach has etiologic and prognostic significance. Proximal lesions are biologically more aggressive and carry a worse prognosis, stage for stage, than distal cancers—a finding that suggests that the pathogenesis differs from that of cancers arising in other parts of the stomach. Distal cancers may be related closely to chronic *H pylori* infection, whereas cardia and gastroesophageal junction cancers may have a different cause, such as chronic gastroesophageal reflux. A contributing factor to the persistently high mortality rate among persons with gastric cancer may be the change since the 1980s in the distribution of cancers from the body and antrum to the proximal stomach. The

incidence of cancers involving the proximal stomach and gastroesophageal junction has increased steadily at a rate exceeding that of any other cancer except melanoma and lung cancer. The reasons for this are unclear. Distal cancers (in the gastric body or antrum) are more common in populations with a high incidence of gastric cancer, whereas cardia cancers are more prevalent in populations with a low incidence of gastric cancer.

Infiltration

Linitis plastica, a diffuse infiltrating form of gastric malignancy, occurs in 5% to 10% of gastric adenocarcinomas. The tumor may extend over a broad region of the gastric wall, resulting in a rigid, thickened stomach; sometimes almost the entire stomach is infiltrated by malignancy. The presence of this lesion at the time of diagnosis is usually associated with locally advanced or metastatic disease and portends a worse prognosis.

Histology

The most widely used histologic classification of gastric adenocarcinoma divides these tumors into 2 types: *intestinal* and *diffuse*. Intestinal-type gastric adenocarcinoma has epithelial cells that form discrete glands, microscopically resembling colonic adenocarcinoma. Typically, the intestinal type is better circumscribed than the diffuse type, and it may be polypoid or ulcerated or both. The intestinal type is the more frequent variety in populations with a high incidence of gastric adenocarcinoma. It often arises within an area of intestinal metaplasia. This pathologic variant generally carries a better prognosis than the diffuse type.

Diffuse-type gastric adenocarcinoma is characterized by sheets of epithelial cells. Glandular structure is rarely present. The diffuse type extends widely, with no distinct margins. Mucus-producing signet ring cells are often present (Figure 6.1). The diffuse type occurs more commonly in younger persons, is less likely to be associated with intestinal metaplasia, and tends to be infiltrating and poorly differentiated; generally, the prognosis is poor.

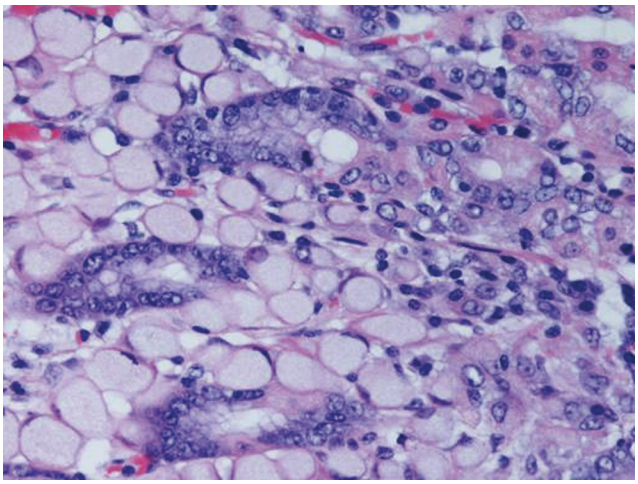

Figure 6.1. Diffuse Type of Gastric Adenocarcinoma With Mucus-Producing Signet Ring Cells. (Courtesy of Thomas C. Smyrk, MD, Anatomic Pathology, Mayo Clinic. Used with permission.)

Staging

Most gastric cancer patients who are symptomatic already have advanced, incurable disease at the time of their initial presentation. The most important aspect of staging is determining whether the cancer is resectable. Clinical stage is determined preoperatively, whereas pathologic staging is based on findings made during surgical exploration and examination of the pathology specimen. The TNM staging system of the American Joint Committee on Cancer, updated in 2010, is used most frequently (Table 6.2). The 2010 update notes that tumors arising at the gastroesophageal junction and those arising in the cardia of the stomach and extending proximally into the gastroesophageal junction are now staged with the TNM system for esophageal cancer rather than for gastric cancer. Tumors that are within 5 cm of the gastroesophageal junction and do not extend into the esophagus are staged as gastric cancers. Also, tumors with positive peritoneal cytology are classified as M1 disease.

Preoperative staging for patients with gastric cancer begins with physical examination. Next, computed tomography (CT) of the chest (for proximal lesions), abdomen, and pelvis is usually the initial imaging test. CT is widely available and is suitable for evaluating widely metastatic disease, especially hepatic involvement, and for assessing ascites or distant nodal spread. Patients who have CT-defined visceral metastatic disease (biopsy proven) can often avoid unnecessary surgery. However, peritoneal metastases are frequently missed with CT.

Another limitation of CT is determination of the depth of tumor invasion, particularly with small tumors. CT is accurate for assessment of the T stage of the primary tumor in about 50% to 70% of cases. Endoscopic ultrasonography (EUS) is the best nonsurgical method for estimating accurately the depth of invasion, particularly for early (T1 or T2) lesions. Although the accuracy of EUS for nodal staging is only slightly better than with CT, EUS-guided fine-needle aspiration of suspicious nodes and regional areas adds to the accuracy of EUS nodal staging; however, this added feature is very operator dependent. Positron emission tomography (PET) or combined PET-CT appears to be more sensitive than CT alone for the detection of distant metastases, but its sensitivity for detecting peritoneal carcinomatosis appears to be limited.

Table 6.2. The TNM Staging System for Gastric Adenocarcinoma

Stage	*Description*
Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria or subserosa
T3	Tumor presents serosa without invasion to adjacent structures
T4	Tumor invades adjacent structures
Nodal (N)	
NX	Regional nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in 1 or 2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in ≥7 regional lymph nodes
Metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis or positive peritoneal cytology

Treatment and Prognosis

Even with more advanced surgical techniques and chemotherapeutic agents, the prognosis for patients with gastric adenocarcinoma remains grim for all but those who are candidates for surgical resection. After resection, the prognosis varies according to the pathologic extent of disease and the population studied. In general, 5-year survival rates for various stages can be approximated as follows: IA, 80% to 95%; IB, 60% to 85%; II, 30% to 50%; IIIA, 20% to 40%; IIIB, 10%; and IV, 7%. In the United States, even with advances in surgical treatment and the use of multimodality therapy, the overall 5-year survival between 2001 and 2007 for all stages combined was only 25% to 30%. The relatively poor prognosis reflects the prevalence of advanced disease at presentation and the aggressive nature of gastric adenocarcinoma.

Surgery is the mainstay of treatment of gastric cancer. Complete surgical removal of a gastric tumor, with resection of the adjacent lymph nodes, offers the only chance for cure. However, two-thirds of patients present with advanced disease that is incurable by surgery alone. This problem is complicated further by a recurrence rate of 40% to 65% among patients who had resection with curative intent.

Controversy persists about what is considered optimal surgical resection, with many different opinions on the extent of resection necessary for cancer found in different parts of the stomach and the extent of lymph node dissection. In practice, the extent of dissection is determined primarily by tumor location, preoperative staging, and the condition of the patient. Proximal gastric tumors require more extensive resection than tumors in the distal stomach. Palliative rather than curative surgery may still be considered in certain circumstances, for example, for tumor obstruction, perforation, or bleeding.

Gastric adenocarcinoma is relatively resistant to radiotherapy, which generally is administered only to palliate symptoms and not to improve survival. Chemotherapeutic regimens have provided only modest results, with a decrease in measurable tumor mass in about 15% of patients and only a minimal effect on prolonging survival.

Gastric Lymphoma

Epidemiology

The gastrointestinal tract is the predominant site of extranodal lymphoma involvement. Primary gastric lymphoma accounts for up to 10% of lymphomas and up to 3% to 5% of gastric neoplasms, and the stomach is the most common extranodal site of lymphoma and accounts for approximately 20% of all extranodal lymphomas. It is also the most common site of gastrointestinal lymphoma. Gastric lymphoma reaches peak incidence in persons between the ages of 50 and 60 years, and, as with gastric adenocarcinoma, there is a slight male predominance. Although these are rare tumors, the incidence of primary gastric lymphoma appears to be increasing, especially among elderly patients.

Risk Factors

There are several risk factors for the development of gastric lymphoma. They include *H pylori*–associated chronic gastritis, autoimmune diseases, immunodeficiency syndromes, long-term immunosuppressive therapy, and celiac disease.

Clinical Features

The clinical features of gastric lymphoma are nonspecific and frequently include abdominal discomfort, anorexia, early satiety, and weight loss as well as gastric outlet complaints due to obstruction or impairment of gastric motility and also anemia due to blood loss from ulceration. Systemic B symptoms (fever and night sweats) are seen in only about 12% of patients.

Diagnostic Evaluation

Endoscopically, gastric lymphoma has a broad range of appearances—from large, firm rugal folds to eroded nodules to exophytic ulcerated masses. Enlarged folds, if present, are due to the subepithelial infiltrative growth pattern of lymphomas.

When the disease is suspected, standard endoscopic biopsy specimens may not be adequate or the histologic findings equivocal, especially when the involvement is primarily submucosal without affecting the mucosa. Deeper biopsy or snare biopsy specimens from a polypoid mass or large rugal fold may be needed to make the diagnosis.

CT of the abdomen and chest is useful in identifying involvement of regional lymph nodes, extension of the tumor into surrounding structures, and distant metastases. If there is no evidence of metastatic disease, EUS is accurate for determining the extent of gastric wall infiltration and can provide useful information for treatment planning. In addition, the pattern seen on EUS may correlate with the type of lymphoma present. In 1 small series, superficial spreading or diffuse infiltrating lesions seen on EUS were due to extranodal marginal zone B-cell lymphomas (ENMZLs) and mass-forming lesions were associated with diffuse large B-cell lymphomas (DLBCLs).

Tumor Features

More than 90% of gastric lymphomas are approximately equally divided into 2 histologic subtypes: low-grade ENMZL of mucosa (gut)-associated lymphoid tissue (MALT) and DLBCL.

Extranodal Marginal Zone B-Cell Lymphoma

ENMZLs of the MALT type, formerly known as MALT lymphoma, constitute a group of low-grade neoplasms that have similar clinical, pathologic, immunologic, and molecular features and arise in the context of preexisting prolonged lymphoid proliferation in mucosal sites. Previously, this disease was often called pseudolymphoma, but it has been classified as a specific subtype of non-Hodgkin lymphoma. MALT lymphomas occur most often in the gastrointestinal tract but have been described in various extranodal sites, including the ocular adnexa, salivary glands, thyroid, lungs, thymus, and breast.

Gastric ENMZLs are associated with *H pylori* infection in as many as 90% of cases. This association has been examined by several investigators, and the mechanism underlying this association is becoming increasingly better understood. In health, the stomach does not have much lymphoid tissue. *Helicobacter pylori*–induced gastritis leads to an aggregation of $CD4^+$ lymphocytes and B cells in the gastric lamina propria. Antigen presentation occurs, followed by T-cell activation, B-cell proliferation, and lymphoid follicle formation. As these follicles become prominent, they develop B-cell monoclonal populations that appear to be sustained by stimuli that come from *H pylori*–sensitized T cells. As the monoclonal B-cell populations proliferate, they begin to spill into the gastric epithelium. In some instances, they evolve into malignant lymphoma cells with uncontrolled growth.

The best evidence supporting the role of *H pylori* in ENMZL in the stomach is remission of the tumor after eradication of *H pylori* infection with antibiotic therapy. Several clinical studies have documented complete remission in approximately 50% of patients with ENMZL and in 80% if the tumor is in an early clinical stage.

Diffuse Large B-Cell Lymphoma

DLBCL describes a heterogenous group of non-Hodgkin lymphoma. DLBCL may occur de novo, but it also may occur as a high-grade transformation from a low-grade B-cell lymphoma such as an ENMZL. Transformation from indolent ENMZL to DLBCL has been described repeatedly in the course of the disease, and some investigators believe that all DLBCLs of the stomach are due to transformation of an ENMZL.

Staging

The staging systems for primary gastric lymphoma are complicated (a variant of the standard staging by lymph node involvement [Figure 6.2]). Generally, stage I disease is limited to the stomach, and stage II disease implies localized involvement of the lymph nodes within the abdomen. In stage III disease, lymph nodes are involved on both the thoracic and abdominal sides of the diaphragm. Stage IV disease is disseminated disease.

Treatment

First-line therapy with antibiotics alone is still considered experimental for gastric ENMZL in patients infected with *H pylori* and should be approached with caution. Most patients who have a response to antibiotics have small flat mucosal lesions and localized disease without lymph node spread or distant metastases. Not all patients are good candidates for monotherapy directed at eradicating *H pylori* infection. Only patients with localized, mucosal, or submucosal flat lesions and without metastatic disease, lymphadenopathy, or frank DLBCL are candidates for antimicrobial therapy alone. For patients who do not meet these criteria, therapy for *H pylori* eradication should be administered in conjunction with conventional therapy.

When treatment of *H pylori* infection has been administered, eradication of the organism must be proven. Histologic regression requires several months after the infection has been cured with antibiotics, and patients require endoscopic follow-up at frequent intervals. If the response to antibiotics is incomplete or the disease recurs, standard therapies for lymphoma, such as systemic chemotherapy, radiotherapy, or surgery, should be administered. Patients who do not initially have a response to anti–*H pylori* therapy or who have disease relapse after therapy still have a high cure rate. For these patients, the 5-year survival rate is as high as 90% after single-agent chemotherapy or radiotherapy. Generally, radiotherapy is the standard of care for patients with localized gastric ENMZL that does not respond to antibiotic therapy or is *H pylori*–negative; the 5-year survival rate is more than 90%. Treatment failures or patients with recurrent or extensive (stage III or IV) disease are treated with multiagent chemotherapy, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).

Conventional therapy for DLBCL depends primarily on the tumor stage. Exploratory laparotomy and partial gastrectomy may be indicated when stage I disease is suspected. For stage II, III, or IV disease, the primary therapy is systemic chemotherapy. Radiotherapy generally is used to reduce the size of large lesions and to control localized disease.

Rituximab (a chimeric monoclonal antibody targeting the CD20 epitope present on virtually all B cells) has demonstrated activity in various types of lymphoma and has been given to patients with ENMZL or DLBCL. Promising results have been reported for a randomized study that compared rituximab plus CHOP (R-CHOP) with CHOP alone in patients who had nodal DLBCL. This study demonstrated improved response rates and survival for the patients randomly assigned to the R-CHOP regimen.

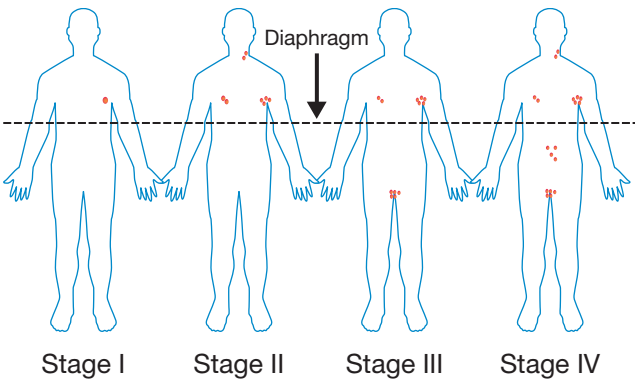

Figure 6.2. Staging Diagram for Lymphoma. Orange marks indicate lymph nodes involved. (Adapted from Patients Against Lymphoma [Internet]. [updated 2013 May 16; cited 2013 Jul 9]. Riegelsville [PA]: Patients Against Lymphoma; c2004. Available from: http://www.lymphomation.org/stage.htm. Used with permission.)

Prognosis

The 5-year survival rate for all patients with gastric lymphoma is 50%. Patients with stage I or II tumors less than 5 cm in diameter have a 10-year survival rate greater than 80%.

Gastrointestinal Stromal Tumors

Stromal or mesenchymal neoplasms affecting the gastrointestinal tract are divided into 2 groups: The less common tumors are identical to those that arise in soft tissues throughout the rest of the body, including lipomas, hemangiomas, schwannomas, leiomyomas, and leiomyosarcomas. The more common tumors are collectively referred to as GISTs.

Epidemiology

GISTs are the most common nonepithelial benign tumor involving the gastrointestinal tract, but they still are rare tumors. The true incidence and prevalence of GIST tumors are unknown because most of them are found incidentally.

On the basis of trials of patients with GISTs, the annual incidence of GIST in the United States is approximately 4,000 to 6,000 new cases. In an autopsy series of patients with gastric cancer, the frequency of incidental subcentimeter GISTs was much higher, which suggests that only a few microscopic tumors grow to a clinically relevant size.

Pathogenesis

Originally, GISTs were thought to be derived from smooth muscle. In the early 1990s, knowledge about GISTs increased

dramatically, and it was discovered that some of the tumors classified as GISTs were truly myogenic, whereas others were neural in origin. Importantly, the almost universal expression of the CD117 antigen by GISTs was identified. This allowed GISTs to be differentiated from leiomyomas and other similar tumors of the gastrointestinal tract.

The CD117 molecule is part of the c-kit receptor, a membrane tyrosine kinase that is a product of the *c-kit* or *KIT* proto-oncogene. In 80% of cases, c-kit activation is the result of an activating *KIT* mutation. It is now thought that the majority (>90%) of mesenchymal tumors arising within the gastrointestinal tract are GISTs.

Previously, GISTs were thought to be benign tumors. Their behavior can be quite variable; however, long-term follow-up studies of patients with GISTs have shown that all GISTs have the potential for malignant behavior.

Clinical Features

Patients with GISTs are often asymptomatic, and the tumors are found incidentally at endoscopy or at surgery. Patients with large GISTs may present with vague symptoms, as with all cancers of the upper gastrointestinal tract, or with gastrointestinal tract bleeding. Cases have been reported of patients with GISTs who present with hypoglycemia due to paraneoplastic production of insulinlike growth factor 2 by the tumor.

Tumor Features

GISTs can arise anywhere in the gastrointestinal tract, but they are most common in the stomach and proximal small bowel. It is uncommon (25% of cases) for them to occur elsewhere in the gastrointestinal tract.

Criteria for distinguishing benign from malignant GISTs, or at least for identifying the tumors most likely to metastasize, have been evaluated but have not been clearly defined. It is known that the larger the tumor, the more likely it will behave in a malignant fashion. It also is understood that the site of origin may predict malignant behavior, with tumors arising from the stomach having less malignant potential than those arising from other locations.

When GISTs metastasize, metastasis is usually to the liver. In contrast to leiomyosarcomas, GISTs rarely spread to regional lymph nodes and virtually never metastasize to distant locations such as the lungs, bones, or brain.

Staging

Staging of GISTs involves primarily endoscopy and imaging studies. As mentioned above, most GISTs occur in the upper gastrointestinal tract and most are discovered incidentally. Endoscopic biopsy specimens obtained with standard techniques typically are not sufficient for definite diagnosis. Although EUS-guided biopsy may not yield enough tissue, specific sonographic features may distinguish GIST from other submucosal lesions (Figure 6.3). CT is the imaging method of choice to characterize large GISTs and to identify metastatic disease. On CT, GISTs appear as a solid mass that enhances brightly with an intravenous contrast agent.

If noninvasive methods are unsuccessful for correctly defining a GIST when it is suspected, preoperative biopsy may not be necessary if the tumor appears to be resectable and the patient is otherwise a surgical candidate. GISTs frequently metastasize to liver and peritoneum and rarely to regional lymph nodes. However, if metastatic disease is present, surgical biopsy may be necessary to confirm the diagnosis if chemotherapy is a consideration.

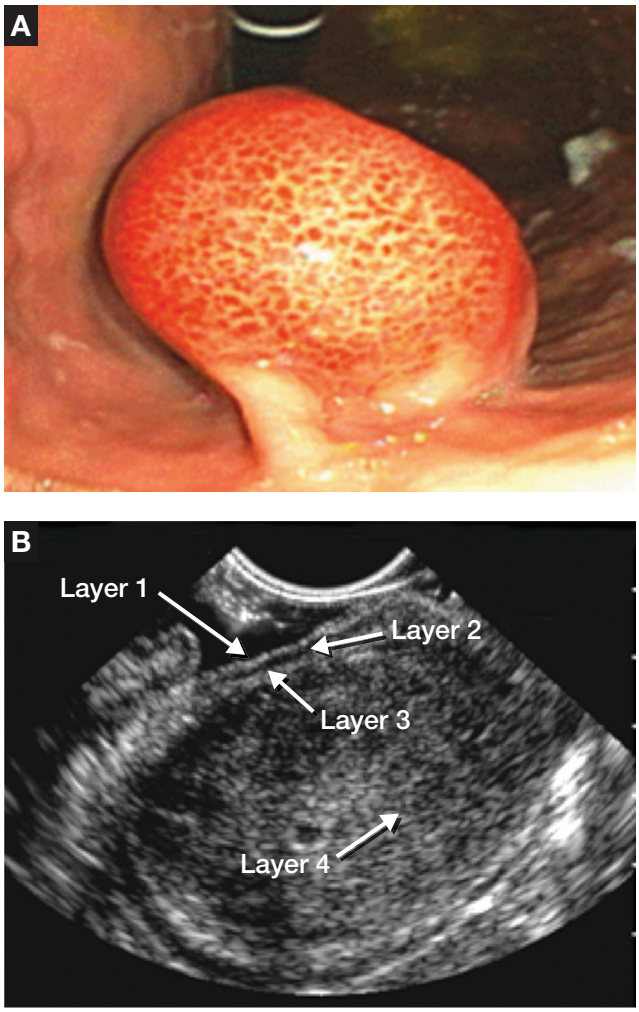

Figure 6.3. Pedunculated Gastric Gastrointestinal Stromal Tumor (GIST). A, Endoscopic image. B, Endoscopic ultrasonographic image. Endoscopic ultrasonography can demonstrate 5 wall layers, but only 4 layers are seen in this image. Layer 1 is hyperechoic (white) and is the superficial mucosal interface. Layer 2 is hypoechoic (black) and is deep mucosa. Layer 3 is hyperechoic and represents the submucosa. Layer 4 is the muscularis propria; it is hypoechoic (black) and is the layer of origin of most GISTs. (Courtesy of Michael J. Levy, MD, Gastroenterology and Hepatology, Mayo Clinic. Used with permission.)

Treatment

Before the year 2000, resection was the only therapy that could be offered to patients with GISTs. The discovery of mutations in the *KIT* gene and the increase in KIT protein function and their association with the oncogenesis of most GISTs was first reported in 1998. Two years later, imatinib mesylate (Gleevec), a potent inhibitor of KIT signaling, was first used. The next 5 years established the safety and efficacy of this drug and demonstrated its clinical impact.

Complete resection is possible for most localized GISTs, but only 50% of patients remain free of disease for more than 5 years. For patients with recurrent disease, locally advanced disease, or metastatic disease, the response rate with imatinib is approximately 80%. Imatinib is not cytotoxic but rather oncostatic. GISTs usually stop growing with this therapy, but they rarely recede or disappear.

Prognosis

Prognosis is influenced by tumor site (small intestine is worse than stomach), tumor size (if larger, the prognosis is worse), the ability to resect the tumor completely, and the response to imatinib in advanced disease. Because this is a rare tumor and treatment has evolved rapidly since 2000, it is difficult to determine an accurate prognosis that would apply to all patients with GIST. In recent reports, 5-year survival rates have ranged from 30% to 100%, depending on the above factors.

Gastroenteric and Pancreatic NETs

Neuroendocrine cells occur throughout the body; for example, they cluster together in small groups called islets throughout the pancreas. NETs can be classified by their site of origin: Those that develop from pancreatic endocrine cells are referred to as pancreatic neuroendocrine tumors (PNETs), and those that originate in the stomach or gut, as gastroenteric neuroendocrine tumors (GNETs).

Classifying NETs further is complex since they arise from many locations, their histologic features are quite varied, and they exhibit a wide range of clinical behaviors. In general, they are separated into 2 major categories:

1. *Poorly differentiated neuroendocrine carcinomas* are high-grade carcinomas that resemble small cell or large cell neuroendocrine carcinoma of the lung. They are associated with a rapidly progressing downhill clinical course and, in general, a poor prognosis.
2. *Well-differentiated NETs of the digestive tract* traditionally include both carcinoid tumors and PNETs.

Although both tumor types have similar histologic characteristics, morphology alone does not predict the clinical course associated with these tumors. They are not a homogenous group clinically, and while most are slow growing and have a relatively indolent course, they display a wide spectrum of biologic and clinical behavior. Up to 40% of patients with GNETs present with liver metastases at the time of diagnosis, but many patients survive for many years even with advanced-stage disease; overall 5-year survival is about 67%.

Epidemiology

Both GNETs and PNETs are relatively rare, with a combined annual incidence in the United States of about 4 per 100,000 to 5 per 100,000 population. The incidence of both has been increasing in the United States and elsewhere; data from the Surveillance, Epidemiology, and End Results (SEER) program showed a 5-fold increase observed since the 1980s. The reasons are not clear, but the increase may be largely due to increased detection on cross-sectional imaging, such as CT or magnetic resonance imaging (MRI), and during endoscopy. However, because GNETs and PNETs are relatively slow growing, their prevalence is much higher and exceeds that of stomach and pancreatic adenocarcinomas combined.

Pathogenesis

Most NETs occur sporadically, although some may appear as part of an autosomal dominant inherited multiple endocrine neoplasia (MEN) syndrome. All NETs can be associated with MEN-1. MEN-1 is characterized by pituitary, parathyroid, and pancreatic hyperplasia or tumors.

Clinical Features

NETs are usually diagnosed in the sixth or seventh decade of life. Because they develop from neuroendocrine cells, they may secrete various peptides and hormones simultaneously. Secreting some of these will not result in clinical symptoms, whereas others, if produced in significant quantities, will result in the appearance of a clinical syndrome.

Carcinoid Tumors and Carcinoid Syndrome

Carcinoid tumors are the most common NET. The greatest occurrence is in the gastrointestinal tract (about two-thirds), while about one-fourth arise in the bronchopulmonary system. They can occur anywhere in the alimentary tract, with the small intestine being the most common site, followed by the rectum and stomach. The clinical manifestation varies from an asymptomatic incidental finding to symptomatic tumors, including the classic carcinoid syndrome.

Clinical and Tumor Features

Most carcinoid tumors are found incidentally; thus, at the time of diagnosis, most patients are asymptomatic. If symptoms are present, they often are nonspecific and associated with the location and extent of the tumor. Symptoms due to the direct effects of a tumor in the gastrointestinal tract may be abdominal pain, intestinal obstruction, nausea, weight loss, or intestinal bleeding. Many patients have vague or mild symptoms for years and are sometimes labeled as having irritable bowel syndrome or other functional disorders of the gastrointestinal tract for years before the correct diagnosis is made.

Most NETs do not produce noticeable symptoms, since the metabolic products are efficiently metabolized by the liver. However, when secreting tumors metastasize to the liver (the most common site of metastasis), substances are released directly into the systemic circulation, circumventing hepatic metabolism. Carcinoid syndrome, which is the primary clinical manifestation, occurs in a subset of patients with carcinoid tumors (8%-35% of patients). When the syndrome is present, it is associated most commonly with tumors in the small bowel; these are the most common and frequently metastasize.

Carcinoid syndrome is due to peptides released by the tumor into the systemic circulation. As many as 40 secretory products have been identified; the common ones are histamine, kallikrein, prostaglandins, serotonin, and tachykinins. The liver is capable of inactivating these peptides, which is the reason patients have symptoms of carcinoid syndrome primarily in association with liver metastases: The bioactive products are secreted directly into the hepatic veins.

The most common symptoms of carcinoid syndrome are diarrhea and facial flushing, followed by cramping abdominal pain, skin telangiectasia, peripheral edema, and wheezing. The most common physical finding is hepatomegaly. Intermittent facial flushing occurs in up to 85% of patients. The flush usually starts suddenly and can last from 30 seconds to 30 minutes. The typical flush is red or violaceous and appears on the face, neck, and upper chest. Flushes can be associated with hypotension and tachycardia. Several inciting factors are known for the flushing associated with carcinoid syndrome: eating, alcohol ingestion, the Valsalva maneuver, increased emotional states, trauma or pressure on the liver (including on physical examination), and

anesthesia. Anesthesia can provoke long episodes of flushing that can result in life-threatening hypotension known as *carcinoid crisis*. Carcinoid crisis can be prevented by the administration of octreotide before anesthesia.

Diarrhea occurs in 80% of patients with carcinoid syndrome and can be quite severe. It is a secretory diarrhea, and patients may pass as many as 30 stools per day. Although the diarrhea usually is unrelated to the flushing episodes, the associated dehydration can contribute to the hypotension from flushing.

Wheezing is a common component of carcinoid syndrome and is due to bronchospasm and right-sided valvular heart disease. Unlike diarrhea, wheezing and dyspnea are worse during flushing episodes. Of importance, wheezing associated with carcinoid syndrome should not be treated like bronchial asthma: Treatment with β-agonists can incite prolonged vasodilation and severe hypotension. Hypertension usually is not present in carcinoid syndrome but, as stated above, the syndrome can cause paroxysmal and clinically important hypotension.

Aside from carcinoid syndrome, the clinical presentation, tumor features, treatment recommendations, and prognosis of carcinoid tumors vary by the location of the primary tumor. Characteristics of carcinoid tumors based on location are outlined in Table 6.3.

Stomach

Gastric carcinoid tumors tend to occur in the body of the stomach. They may be single or multiple, and, to endoscopists, they may appear to be an ordinary ulcer, polyp, or tumor mass. They are often round and gray or yellow.

Gastric carcinoid tumors occur more frequently in patients who have a disease that causes hypergastrinemia, such as pernicious anemia or atrophic gastritis with achlorhydria. They also appear to be more common in patients with Zollinger-Ellison syndrome. Any condition in which serum levels of gastrin are increased for a prolonged period should alert clinicians that gastric carcinoid tumors may be present.

Gastric carcinoids have been divided into 3 types, each of which has a different behavior and prognosis.

Type 1

Up to 80% of all gastric carcinoids are type 1. They are associated with pernicious anemia or chronic atrophic gastritis. The tumors are derived from enterochromaffin-like cells and are thought to develop from long-standing stimulation by increased serum levels of gastrin. Type 1 carcinoids usually are diagnosed in patients in their 60s and 70s. As with chronic atrophic gastritis and pernicious anemia, type 1 carcinoids are more common in women than in men. These tumors are usually small and multiple. Metastatic disease is rare and occurs in less than 10% of tumors 2 cm or smaller but in as many as 20% of larger tumors. These tumors generally are indolent and often are considered a benign condition.

Type 2

Carcinoid tumors of the stomach due to hypergastrinemia from gastrinomas are classified as type 2 gastric carcinoids. They are rare (<5% of gastric carcinoids) and, like type 1 gastric carcinoids, they are typically small, multiple, slow growing, and indolent and have little malignant potential.

For types 1 and 2 gastric carcinoids smaller than 1 cm, endoscopic resection, if possible, is the treatment of choice. Because these patients often have sustained hypergastrinemia, endoscopic surveillance every 6 to 12 months has been recommended, but progression to malignant disease and death is unusual.

For patients with multiple tumors or advanced disease that is not appropriate for resection, antrectomy or medical therapy aimed at reducing serum levels of gastrin has been advocated. Antrectomy decreases hypergastrinemia by removing much of the gastrin-producing cell mass in the stomach. In a small controlled study, this was shown to lead to regression of these tumors.

Type 3

Type 3 gastric carcinoids are sporadic and do not appear to be associated with hypergastrinemia. Of all gastric carcinoids, 20% are type 3. They are the most aggressive of the gastric carcinoids, and 65% of patients have local or liver metastases when the tumor is discovered. Type 3 is the only type of gastric carcinoid that is associated with carcinoid syndrome; these tumors often produce 5-hydroxytryptophan. Because sporadic gastric carcinoids (type 3) are more aggressive, they usually are treated with partial or total gastrectomy with local lymph node resection.

Overall, patients who have carcinoid tumors arising in the stomach have a 5-year survival rate of 50% to 95%.

Small Intestinal Carcinoid Tumors

Clinically, small intestinal carcinoid tumors are the most important carcinoid tumors because patients are more likely to present with intestinal symptoms and carcinoid syndrome, which occurs in up to 10% of these patients. Abdominal pain or bowel obstruction can be caused by the direct mechanical effect of the tumor and an associated fibroblastic reaction, intussusception, or mesenteric ischemia due to tumor-associated fibrosis or angiopathy.

Most small intestinal carcinoids occur in the ileum within 0.6 m of the ileocecal valve. Carcinoids that occur in the small intestine may be multicentric and have a higher likelihood than carcinoids arising from other portions of the gastrointestinal tract to metastasize to regional lymph nodes and the liver. Because

Table 6.3. Characteristics of Carcinoid Tumors Based on Location

Location	*Secretory Products*	*Carcinoid Syndrome*	*Clinical Characteristics*
Foregut			
Stomach, duodenum, pancreas	Serotonin, histamine	Rare	Indolent except type 3 gastric carcinoid
Midgut			
Jejunum, ileum, appendix, ascending colon	Serotonin, prostaglandins, polypeptides	Classic, but present in <10% of cases	Often multiple, usually in ileum
Hindgut			
Transverse colon, descending colon, sigmoid colon, rectum	None	Rare	Indolent except in colon

small intestinal carcinoids, regardless of size, have the potential to metastasize, they should be removed surgically, with local lymph node resection. Patients with these tumors are most at risk for synchronous lesions (present in 30% of cases), so at surgery, the surgeon should thoroughly inspect the remaining small bowel. Resection may be required for palliation, even in patients with metastatic disease. The prognosis for patients with small intestinal carcinoids varies with the stage of disease. The 5-year survival rate ranges from 35% to 80%.

Appendix

Up to one-half of intestinal carcinoids are appendiceal tumors, and carcinoid tumors are the most common neoplasms of the appendix. Patients are almost always asymptomatic, and typically these tumors are discovered incidentally at appendectomy. Incidental carcinoids are found in 0.5% of appendectomy specimens. Appendiceal carcinoids are often smaller than 1 cm. They usually are solitary and benign. Although local invasion by appendiceal carcinoids is common, metastatic disease is rare.

If symptoms are present, they usually are associated with large tumors, tumors located at the base of the appendix, and those that have associated metastatic disease. Approximately 10% of patients with appendiceal carcinoids have tumors at the base of the appendix, where the tumor can cause obstruction that may result in appendicitis. Patients with appendiceal carcinoids may present with carcinoid syndrome, but this occurs almost always with liver metastases.

The prognosis for patients with appendiceal carcinoids is determined by the size of the tumor. Tumors smaller than 2 cm (most tumors) are unlikely to have metastasized when diagnosed. Tumors larger than 2 cm are uncommon, but when they are present, up to 30% have metastasized at the time of diagnosis. Appendiceal tumors smaller than 2 cm can be treated with simple appendectomy. However, for larger tumors, right hemicolectomy should be performed.

The overall 5-year survival rate for patients with appendiceal carcinoids is 70% to 100%, but for patients with metastatic disease at the time of presentation, it ranges from 10% to 30%.

Colon

Carcinoid of the colon is rare. When it occurs, it is often located on the right side of the colon. Unlike patients with carcinoid tumors in other locations, those with carcinoid of the colon may present with symptoms, and when they do, they often have locally advanced disease. Local resection of the tumor has been reported to be effective in the early stages of disease, but many patients require radical colectomy because of advanced disease at the time of diagnosis. Patients with colonic carcinoid tumors rarely have carcinoid syndrome. The overall 5-year survival rate for patients with colonic carcinoid tumors is 30% to 75%.

Rectum

Patients with rectal carcinoids nearly always are asymptomatic, and the tumors are found incidentally during proctosigmoidoscopy. They are not associated with carcinoid syndrome. Tumors smaller than 1 cm can be treated with local excision. Radical excision is more appropriate for tumors larger than 2 cm or for smaller tumors that have invaded the muscularis propria. The overall 5-year survival rate for patients with rectal carcinoid tumors ranges from 75% to 100%.

Diagnosis of Carcinoid Tumors and Carcinoid Syndrome

Most carcinoid tumors are found incidentally on endoscopy or cross-sectional imaging, such as CT performed for other indications. If symptoms of carcinoid syndrome are strongly suspected, the best initial evaluation is to measure urinary 5-hydroxyindoleacetic acid (5-HIAA), which is the end product of serotonin metabolism. This test has a sensitivity of more than 90% and a specificity of 90% for carcinoid syndrome. Sensitivity is lower for patients who have carcinoid tumors without symptoms of carcinoid syndrome. Measurement of urinary excretion of 5-HIAA is generally most useful in patients with primary midgut (small bowel and right colon) tumors, which tend to produce the highest levels of serotonin. The normal rate of excretion of 5-HIAA over 24 hours is 2 to 8 mg daily. The rate of excretion may be up to 30 mg daily in patients with malabsorption syndromes such as celiac disease and Whipple disease, as well as after the ingestion of large amounts of tryptophan- or serotonin-rich foods. Patients should avoid the ingestion of tryptophan- and serotonin-rich foods, such as banana, tomato, avocado, and certain nuts at least 24 hours before and during the 24-hour urine collection.

Chromogranins are proteins that are stored and released with peptides and amines in various neuroendocrine tissues and are designated as chromogranin A (CgA), B, and C. Well-differentiated NETs, such as carcinoids, are associated with elevated blood concentrations of chromogranins, which increase with a larger tumor burden. CgA is a more sensitive indicator of a NET than chromogranin B or C. Levels of CgA vary daily in healthy subjects and in those with NETs. False-positive elevations of CgA can be present in various other conditions, including inflammatory conditions and endocrine, gastrointestinal, and cardiovascular diseases and as a result of medications, such as histamine$_2$-receptor antagonists and proton pump inhibitors. Because of its low specificity, measurement of CgA alone is not recommended as a screening test for the diagnosis of a carcinoid tumor or carcinoid syndrome. However, for patients with an established diagnosis, CgA can be used as an appropriate tumor marker to assess disease progression or response to therapy or after surgical resection.

Carcinoid tumors are highly vascular, and those that originate in the small intestine often produce mesenteric masses with dense desmoplastic fibrosis. These features are usually well seen on CT or MRI scans of the abdomen and pelvis. Both imaging modalities can demonstrate liver metastases, although MRI is probably more sensitive than contrast-enhanced CT. Many carcinoid tumors express high levels of somatostatin receptors and can therefore be imaged with somatostatin receptor scintigraphy (SRS) and a radiolabeled form of the somatostatin analogue octreotide (Octreoscan). This technique has the advantage of providing whole body scanning, which allows detection of metastases outside the abdominal region. However, poorly differentiated NETs express low somatostatin-receptor levels and are unlikely to be detected on SRS imaging.

Pancreatic Neuroendocrine Tumors

The vast majority of pancreatic malignancies are adenocarcinomas and arise from pancreatic exocrine cells. PNETs make up less than 4% of all diagnosed pancreatic cancers. These malignancies may progress and the tumor cells may spread to other organ sites, such as to lymph nodes near the pancreas or to the liver, lung, peritoneum, or bone. Advanced PNETs may be either *functional*

or *nonfunctional*. Functional PNETs produce hormones such as gastrin, insulin, or glucagon, which are released into the blood and cause symptoms. Nonfunctional PNETs are more difficult to diagnose, since they produce substances that often do not cause overt symptoms until the tumor spreads and continues to grow. PNETs include the following: gastrinoma, insulinoma, VIPoma, glucagonoma, and somatostatinoma.

Gastrinoma

Gastrinomas produce the classic triad of symptoms called *Zollinger-Ellison syndrome*. This syndrome consists of peptic ulcer disease, gastric acid hypersecretion, and a gastrin-producing tumor. Gastrinomas are rare and occur in less than 1% of patients who have peptic ulcer disease. Gastrinomas are associated frequently with MEN-1 syndrome.

Etiology and Pathogenesis

The majority of gastrinomas were thought to be nonislet cell tumors of the pancreas. With advances in technology, extrapancreatic gastrinomas are now known to be common. One-half of gastrinomas occur in the duodenal wall; the pancreas is the second most common site. However, 90% of gastrinomas occur in an anatomical area called the *gastrinoma triangle* (Figure 6.4).

Gastrinomas are slow growing, and it can be difficult to distinguish benign tumors from malignant ones. Approximately two-thirds of gastrinomas are malignant. The best indicator of malignancy is the presence of metastases, which most often affect the regional lymph nodes or the liver. It is important to determine whether liver metastases are present. If they are, the patient is not a candidate for surgical treatment.

Clinical Features

Peptic ulcer disease is the most common sign of gastrinoma and occurs in more than 90% of patients. Traditionally, the ulcer disease associated with gastrinomas has been characterized by multiple duodenal ulcers (including postbulbar ulcers) and esophagitis that is refractory to medical treatment (Figure 6.5). However, the most common type of ulcer associated with gastrinoma is an ordinary ulcer in the duodenal bulb.

As many as 70% of patients with a gastrinoma have symptoms or endoscopic findings of severe gastroesophageal reflux, which likely is caused by hypersecretion of gastric acid. Also, 50% of the patients have diarrhea due to the effect of acid hypersecretion on the small bowel. Increased acid exposure to the small bowel causes morphologic and inflammatory changes that can result in malabsorption. In addition, the low pH may inactivate pancreatic lipase and cause bile salts to precipitate, resulting in malabsorption of fat and steatorrhea.

If a patient has a duodenal ulcer that is not caused by either *H pylori* infection or nonsteroidal antiinflammatory drugs or if a patient has duodenal ulcer disease and diarrhea, the concurrent presence of gastrinoma should be considered.

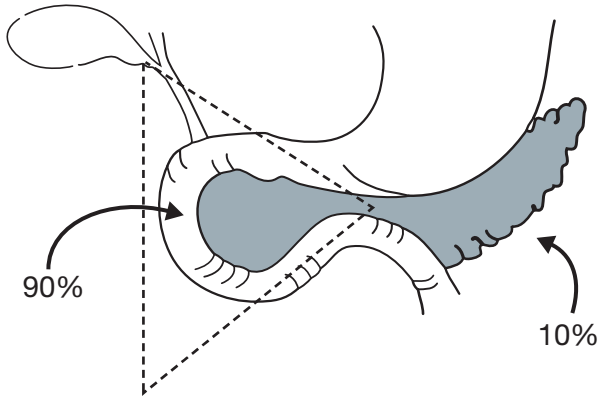

Figure 6.4. The Gastrinoma Triangle. Most gastrinomas (90%) occur inside this triangle.

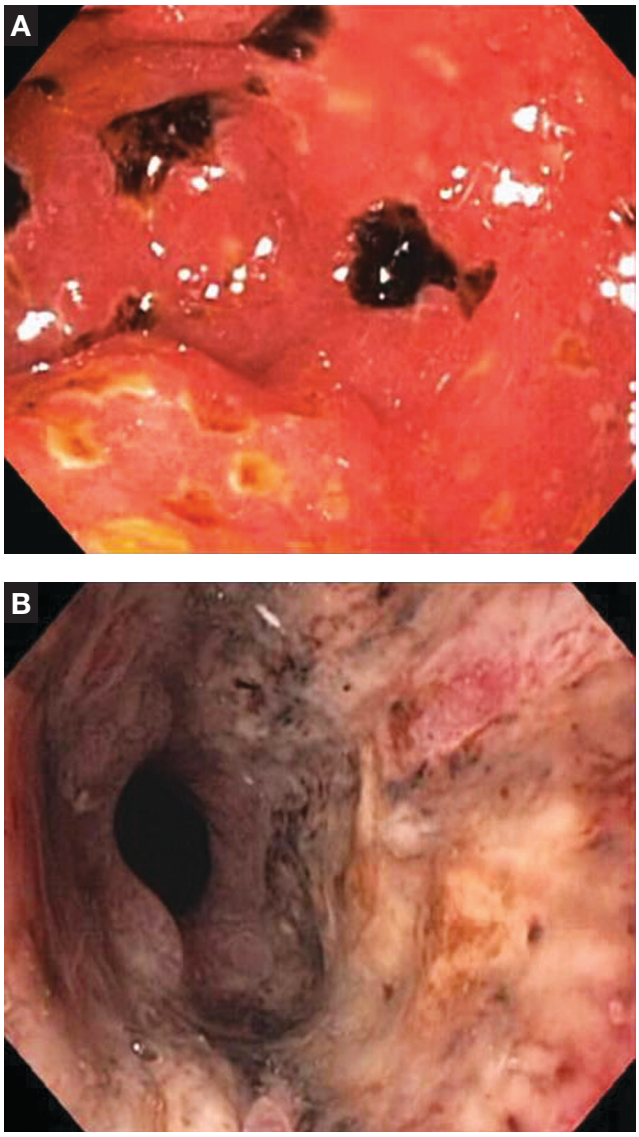

Figure 6.5. Endoscopic Images From a Patient With Metastatic Gastrinoma. The patient was receiving proton pump inhibitor therapy. A, Multiple duodenal ulcers. B, Severe esophagitis.

Diagnostic Tests

For patients with the clinical manifestations of gastrinoma, the first screening test is measurement of the serum level of gastrin. This should be done after proton pump inhibitor therapy has been withheld for at least 7 days. A serum gastrin level of more than 1,000 pg/mL suggests the presence of a gastrinoma. A level less than 1,000 pg/mL but more than 110 pg/mL may be

consistent with several conditions that cause hypergastrinemia. The most common cause of hypergastrinemia generally is achlorhydria. The most common cause of achlorhydria, in turn, is atrophic gastritis. Other causes of hypergastrinemia associated with achlorhydria include gastric ulcer, gastric carcinoma, vagotomy, and current proton pump inhibitor therapy. Also, some disorders cause hypergastrinemia with normal or increased acid secretion. These are gastric outlet obstruction, retained gastric antrum in patients with previous gastric surgery, and a rare hereditary condition called *antral G cell hyperplasia*.

A gastric pH probe can be used to determine whether acid hypersecretion is present. For a patient who has not been receiving proton pump inhibitor therapy for at least 7 days, gastric pH less than 4 is consistent with a hypersecretory condition, and this, in combination with a markedly increased gastrin level, is highly suggestive of Zollinger-Ellison syndrome.

A secretin stimulation test is warranted for only a few clinical situations (Figure 6.6). If a patient has pronounced hypergastrinemia and acid hypersecretion (not achlorhydria) but the serum gastrin level is less than 1,000 pg/mL, an intravenous secretin test is indicated. In patients with Zollinger-Ellison syndrome, the serum level of gastrin increases at least 200 pg/mL over the basal gastrin level. Patients with other causes of hypergastrinemic hyperchlorhydria have only a slight or no increase in the serum level of gastrin.

After there is biochemical evidence of gastrinoma, the tumor should be localized. Most gastrinomas have somatostatin receptors. SRS with the radiolabeled somatostatin analogue octreotide can localize 85% of gastrinomas. Because most gastrinomas occur in the gastrinoma triangle, EUS is very sensitive in localizing the primary tumor but is less helpful in evaluating metastatic disease. CT of the abdomen detects approximately one-half of the tumors and may be useful for directing biopsy of liver metastases, if present.

Treatment

Surgical resection is the treatment of choice for patients with resectable (ie, not metastatic or locally advanced) disease. Patients with liver metastases or MEN-1 syndrome (with multifocal disease) may not be candidates for surgical treatment because they may have multiple tumors.

If resection is not possible, the objective in treating Zollinger-Ellison syndrome is to control gastric acid hypersecretion. Medical treatment to decrease gastric acid hypersecretion usually consists of high-dose proton pump inhibitors; often a gradual dose reduction is possible. The administration of octreotide, which inhibits the secretion of gastrin, often produces an unpredictable clinical response and generally is not considered first-line therapy.

Insulinoma

Insulinomas are insulin-secreting islet cell tumors that originate in the pancreas and cause symptoms of hypoglycemia. They are usually solitary but, rarely, may be multiple.

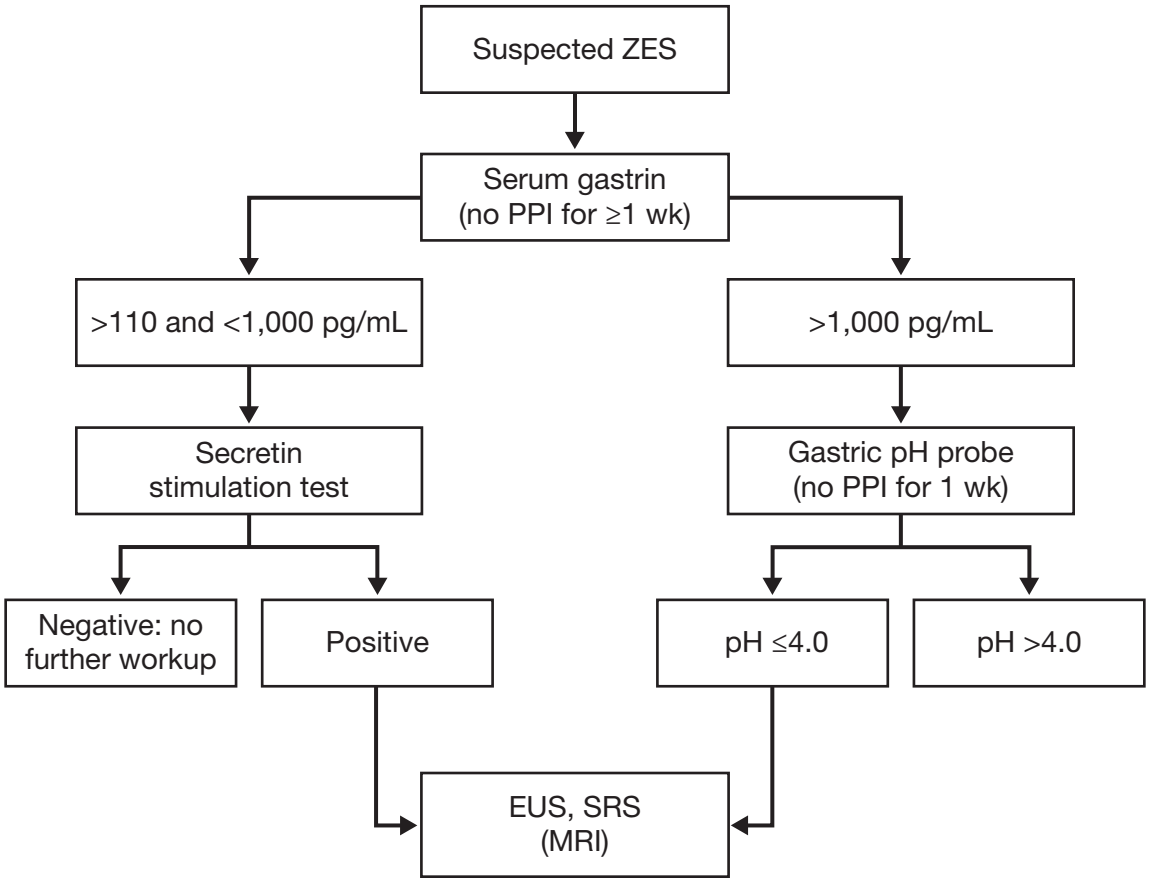

Figure 6.6. Diagnostic Evaluation of Gastrinoma and Zollinger-Ellison Syndrome (ZES). EUS indicates endoscopic ultrasonography; MRI, magnetic resonance imaging; PPI, proton pump inhibitor; SRS, somatostatin receptor scintigraphy.

Clinical Features

Most patients present with clinical manifestations of hypoglycemia: altered or loss of consciousness, confusion, dizziness, and visual disturbances. Symptoms may result also from catecholamine release caused by hypoglycemia. These symptoms are anxiety, weakness, fatigue, headache, palpitations, tremor, and sweating. Typically, symptoms occur with fasting, when a meal is delayed or missed, or during exercise. Patients may learn to avoid symptoms by eating frequently; as a result, 40% of patients have a history of weight gain from increased eating.

Diagnosis

The presence of an insulinoma is determined by the combination of a low fasting blood glucose level and an inappropriately increased plasma level of insulin. This combination is identified in 65% of patients with insulinoma. For a definitive diagnosis, a 72-hour fast is required, with the serum levels of glucose and insulin determined at regular intervals and when the patient becomes symptomatic. With this fasting test, symptoms develop in 75% of the patients with an insulinoma within 24 hours, in 95% by 48 hours, and in virtually 100% within 72 hours.

When there is biochemical evidence of an insulinoma, localization of the tumor can be difficult because most tumors are small. Because it is less common for insulinomas than for gastrinomas to have somatostatin receptors, SRS with radiolabeled octreotide can localize only 50% of the tumors. Also, CT of the abdomen detects only 50% of insulinomas because of their small size. These tumors are almost exclusively in the pancreas, and EUS has become the imaging modality of choice, detecting nearly 90% of pancreatic insulinomas. Metastatic insulinoma is evaluated best with MRI.

Treatment

As for any GNET, definitive treatment is surgical removal of the tumor, and this is indicated for any patient in whom metastatic disease has not been identified. According to most reports, 70% to 95% of all patients are cured with surgical treatment.

Patients with metastatic disease and those with insulinomas that have not been removed by partial pancreatectomy can be managed with hyperglycemic agents such as diazoxide and octreotide. Also, patients with metastatic insulinoma may receive chemotherapy. The most effective combination chemotherapy is streptozocin and doxorubicin.

VIPoma

VIPoma syndrome is caused by an NET that produces vasoactive intestinal polypeptide (VIP). VIP induces intestinal water and chloride secretion and inhibits gastric acid secretion. This syndrome is characterized by severe watery diarrhea, hypokalemia, and achlorhydria and is known as the *WDHA* (*w*atery *d*iarrhea, *h*ypokalemia, and *a*chlorhydria) *syndrome* or Verner-Morrison syndrome.

Pathogenesis

Approximately 90% of VIPomas are in the pancreas. Although other tumors, including intestinal carcinoids, pheochromocytomas, and bronchogenic carcinomas, may produce VIP, they rarely cause VIPoma syndrome. VIPomas are usually solitary non-beta pancreatic islet cell tumors, and more than 75% of them occur in the body or tail of the pancreas. Although these tumors are slow growing, they frequently reach a large size before diagnosis; 75% of VIPomas are malignant, and 50% have metastasized at the time of diagnosis. VIPomas cannot be distinguished from other pancreatic endocrine tumors with conventional histologic or electron microscopic examination. However, the demonstration of immunoreactive VIP in the tumor and plasma establishes the diagnosis.

Clinical Features

As stated above, VIPomas cause secretory diarrhea, which results in hypokalemia and dehydration. Stool volume may exceed 3 L daily. The watery diarrhea resembles that of cholera, hence the term *pancreatic cholera* is sometimes used. Erythematous flushing of the head and trunk may occur in some patients. Also, hyperglycemia develops in some patients because of VIP- and hypokalemia-induced glycogenolysis in the liver.

Diagnosis

VIPoma syndrome should be suspected if patients present with high-volume watery diarrhea that persists despite fasting and is associated with hypokalemia and dehydration. The diagnosis is confirmed by the finding of an increased plasma concentration of VIP. Because these tumors are large, frequently malignant, and metastatic, the abdomen should be scanned with CT to localize and determine the extent of tumor involvement. MRI is also effective for localizing the tumor and demonstrating metastatic disease. Other imaging studies may not be necessary. Preliminary data indicate that SRS and EUS also are effective for imaging these tumors.

Treatment

The first priority of treatment is to correct the dehydration and electrolyte abnormalities. Patients may require at least 5 L of fluid daily with aggressive potassium replacement. Long-acting octreotide controls diarrhea in most patients with VIPoma, and this agent is considered the initial treatment of choice. For patients who do not have a response to somatostatin analogues, concomitant administration of glucocorticoids may be tried because the combination has had some success.

After imaging studies have localized and determined the extent of tumor involvement, surgery should be considered for all patients who do not have evidence of metastatic disease. Surgical resection of a pancreatic VIPoma relieves all symptoms and is curative in approximately 30% of patients. Surgery also may be indicated to relieve local effects produced by the large size of the tumor.

For patients with metastatic disease, the best treatment option is chemotherapy. The most effective chemotherapy regimen is streptozocin in combination with either doxorubicin or fluorouracil, which achieves partial remission in up to 90% of patients.

Glucagonoma

Glucagonomas produce a rare syndrome of dermatitis, glucose intolerance, weight loss, and anemia associated with a pancreatic islet cell tumor.

Pathogenesis

Glucagonomas usually are solitary, large tumors with an average size of 5 to 6 cm at the time of diagnosis; 65% are located in the head of the pancreas, and the other 35% occur equally in the body and tail. Most tumors are metastatic at the time of diagnosis.

Clinical Features

Glucagonomas occur in persons 45 to 70 years old. Typically, the patient presents with a distinct dermatitis called *necrolytic migratory erythema*, which usually develops a mean of 7 years before the onset of other symptoms. This rash starts as an erythematous area, typically in an intertriginous area such as the groin, buttocks, thighs, or perineum, or it may start in periorificial areas. The erythematous lesions spread laterally and then become raised, with superficial central blistering or bullous formation. When the bullae rupture, crusting occurs and the lesions begin to heal in the center. Healing is associated with hyperpigmentation. The entire sequence usually takes 1 to 2 weeks and consists of a mixed pattern of erythema, bullous formation, epidermal separation, crusting, and hyperpigmentation, which wax and wane. Glossitis, angular stomatitis, dystrophic nails, and hair thinning are other clinical findings. The majority of patients with glucagonoma also have hypoaminoacidemia, which may be responsible for the rash. The rash improves with treatment with amino acids and nutrition.

Glucagon stimulates glycogenolysis, gluconeogenesis, lipolysis, ketogenesis, and insulin secretion and inhibits pancreatic and gastric secretion and intestinal motility. Most patients have glucose intolerance, and some may have frank diabetes mellitus. Most patients with glucagonoma also have noticeable weight loss, even if the tumor is found incidentally and is small. It is believed that glucagon exerts a catabolic effect. Some patients also may have anorexia.

Diagnosis

If the clinical features of glucagonoma are present, the diagnosis can be confirmed by the finding of an increased plasma glucagon level of more than 1,000 pg/mL. Because glucagonomas occur in the pancreas and tend to be large and metastatic at the time of clinical presentation, CT of the abdomen usually localizes the tumor.

Treatment

The initial treatment objectives are to control the symptoms and hyperglycemia and to restore the nutritional status. The surgical risk for these patients usually is increased because of the catabolic effects of glucagon, glucose intolerance, and hypoaminoacidemia. Patients should receive nutritional support, and the hyperglycemia should be corrected. The rash may improve with correction of the hypoaminoacidemia. If anemia is pronounced, transfusion may be needed. Octreotide is useful for controlling symptoms, and it improves the dermatitis, weight loss, diarrhea, and abdominal pain but not diabetes mellitus. Surgery is offered to all patients who are acceptable surgical risks and who do not have evidence of metastatic spread of the tumor, but it is curative in only 20% of them.

For patients with metastatic disease, it is important to remember that the tumors are slow growing and survival is good even for those who do not receive chemotherapy. There is no clear evidence that chemotherapy has any important effect on these tumors. The most commonly used chemotherapeutic agents are streptozocin in combination with either doxorubicin or fluorouracil.

Somatostatinoma

Somatostatinomas are the least common of the GNETs. They produce a distinct syndrome of diabetes mellitus, gallbladder disease, and steatorrhea.

Pathogenesis

Somatostatinomas are NETs that occur in the pancreas and intestine. Tumors that arise in the pancreas tend to have higher levels of somatostatin and are more likely to produce symptoms. Somatostatinomas are usually solitary and large, and the majority have metastasized at the time of diagnosis. Somatostatin inhibits insulin release, gallbladder motility, and secretion of pancreatic enzymes and bicarbonate.

Somatostatinomas are not associated with MEN-1. However, they have been found in patients with pheochromocytoma, café au lait spots, and neurofibromatosis, suggesting a possible association with MEN-2B.

Clinical Features

Diabetes mellitus occurs in one-half of the patients with somatostatinoma. Gallbladder disease occurs in 65% of the patients and usually is manifested as cholelithiasis, acalculous cholecystitis, or obstructive jaundice from local tumor invasion. Steatorrhea occurs in one-third of the patients.

Diagnosis

Most somatostatinomas are found incidentally when laparotomy is performed for gallbladder disease. The diagnosis is established by the finding of somatostatin-containing D cells in the resected tumor and an increased plasma concentration of somatostatin-like immunoreactive material. Tumors are localized with CT, EUS, or ultrasonography of the abdomen.

Treatment

Diabetes mellitus usually is mild and responds to oral hypoglycemic agents or low doses of insulin. No specific medical treatment exists for treating somatostatinomas. Octreotide may be helpful in treatment. However, somatostatinomas are rare, and more reports are needed to determine the efficacy of octreotide.

Surgical excision is the treatment of choice, but most patients present with metastatic disease. Cytotoxic chemotherapy is offered to patients who have evidence of metastatic disease, but there is no clear evidence that this treatment is effective.

Management Principles for GNETs and PNETs

In general, the treatment of GNETs and PNETs is based on the following: localization of the tumor and identification of metastatic disease if present, resection of the primary tumor if appropriate, and control of symptoms, such as those associated with carcinoid syndrome (Figure 6.7).

The liver is the predominant site of metastatic disease. Liver resection is indicated for the treatment of metastatic liver disease in the absence of diffuse bilobar involvement, compromised liver function, or extensive extrahepatic metastases. Although surgery is not curative in the majority of cases, symptoms of hormone hypersecretion are effectively palliated and prolonged survival is often possible because these tumors are slow growing.

Other therapies can be directed at specific components of the syndrome. Carcinoid syndrome patients with flushing should avoid ingesting substances, such as alcohol, that can induce flushing. Also, physical therapy that could involve pressure or trauma to the right upper quadrant should be avoided. Certain drugs, such as codeine and cholestyramine, can help control flushing

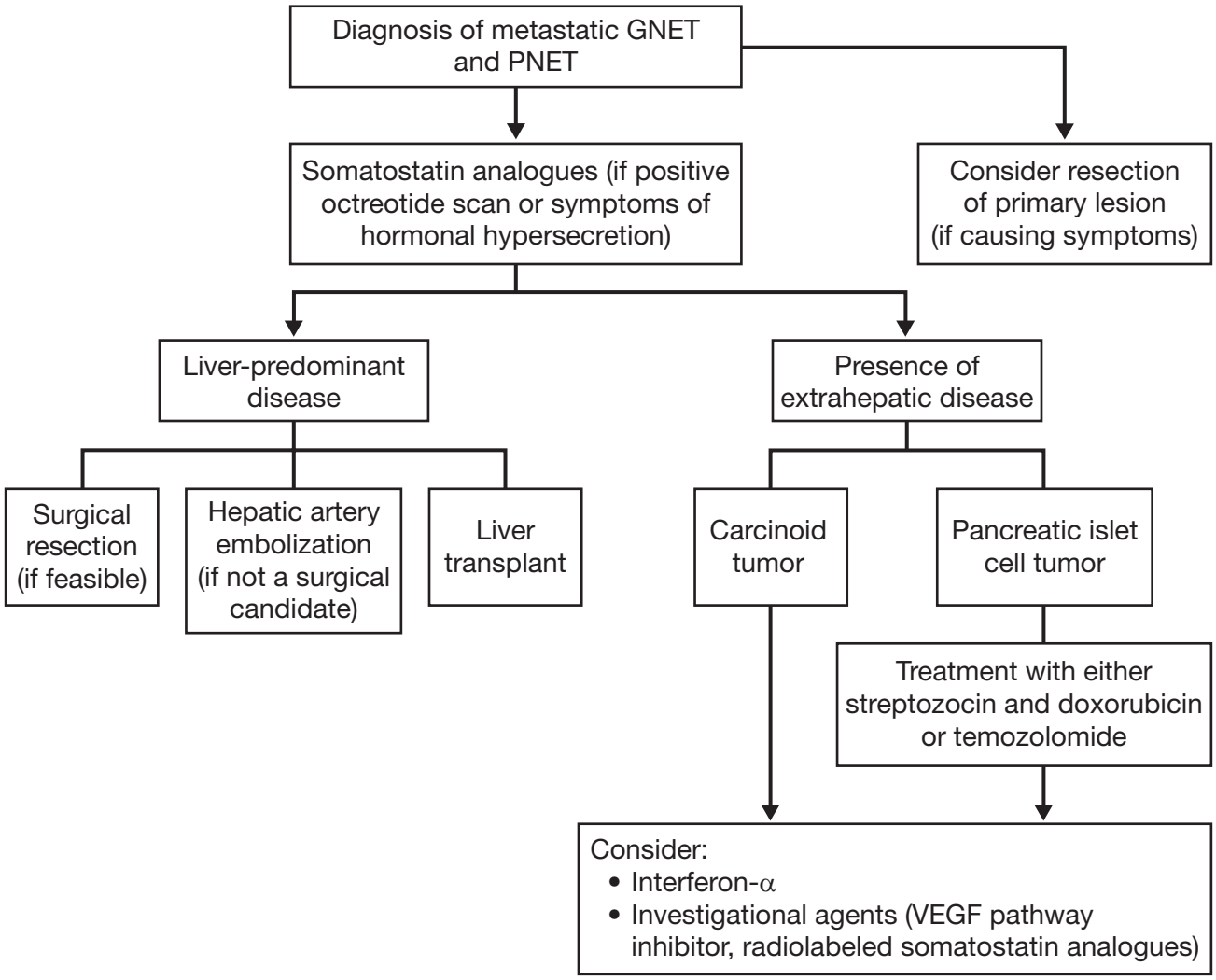

Figure 6.7. Treatment Algorithm for Metastatic Gastroenteric Neuroendocrine Tumor (GNET) and Pancreatic Neuroendocrine Tumor (PNET). VEGF indicates vascular endothelial growth factor.

and diarrhea. Severe symptoms often require a somatostatin analogue such as octreotide.

Flushing and diarrhea can be ameliorated in up to 80% of patients treated with octreotide. A depot form of octreotide (Sandostatin LAR) has been developed that allows for administration monthly, rather than 3 times daily. Typically, patients start a brief trial of the short-acting form of octreotide (to assess for symptomatic response and tolerance) and then start receiving a dose of 20 mg intramuscularly monthly, with a gradual increase in the dose as needed for control of symptoms. Patients also can be given short-acting, subcutaneous octreotide for breakthrough symptoms.

In addition to improving symptoms, octreotide may retard tumor growth. Because octreotide is not cytotoxic, the disease rarely regresses.

Patients who have progressive metastatic carcinoid tumors have few therapeutic options, and the best systemic therapy has not been defined. Several cytotoxic drugs (streptozocin in combination with either doxorubicin or fluorouracil) have been tried in various combinations and generally have had minimal effect on these tumors. The lack of effectiveness of any 1 agent or combination of agents has led to debate about whether chemotherapy is appropriate for these patients.

Metastatic Disease to the Stomach

When a patient presents with upper gastrointestinal tract symptoms and a history of a primary extragastric neoplasm, metastatic involvement of the stomach should be considered as a possible explanation of the symptoms.

Malignant melanoma is one of the most frequently encountered metastatic lesions to the stomach. At endoscopy, it usually appears as a slightly elevated black nodule. Cancer of the breast, lung, ovary, testis, liver, or colon or sarcoma can all involve the stomach.

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7

Gastrointestinal Motility Disorders[a,b]

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Motility disorders result from impaired control of the neuromuscular apparatus of the gut. Associated symptoms include recurrent or chronic nausea, vomiting, bloating and abdominal discomfort, constipation, or diarrhea, which occur in the absence of a structural lesion. Occasionally, gastroparesis and intestinal pseudo-obstruction are associated with generalized disease processes that affect other regions of the gastrointestinal tract and extraintestinal organs, including the urinary bladder. For many people, the role of motility in generating symptoms is unclear. Patients who have similar symptoms are thought to have a functional gastrointestinal disorder, specifically functional dyspepsia.

Control of Gastrointestinal Motor Function

Motor function of the gastrointestinal tract depends on the contraction of smooth muscle cells and their integration and modulation by enteric and extrinsic nerves and on the pacemaker cells in the wall of the gut, called the interstitial cells of Cajal. Derangement of the mechanisms that regulate gastrointestinal motor function may lead to altered gut motility. Neurogenic modulators of gastrointestinal motility include the central nervous system, the autonomic nerves, and the enteric nervous system. Extrinsic neural control of gastrointestinal motor function consists of the cranial and sacral parasympathetic outflow (excitatory to nonsphincteric muscle) and the thoracolumbar sympathetic supply (excitatory to sphincters and inhibitory to nonsphincteric muscle). The cranial outflow is predominantly through the vagus nerve, which innervates the gastrointestinal tract from the stomach to the right colon and consists of preganglionic cholinergic fibers that synapse with the enteric nervous system. The supply of sympathetic fibers to the stomach and small bowel arises from levels T5 to T10 of the intermediolateral column of the spinal cord. The prevertebral ganglia have an important role in the integration of afferent impulses between the gut and the central nervous system and reflex control of abdominal viscera.

The enteric nervous system is an independent nervous system consisting of approximately 100 million neurons organized into ganglionated plexuses. The larger myenteric (or Auerbach) plexus is situated between the longitudinal and circular muscle layers of the muscularis externa and contains neurons responsible for gastrointestinal motility. The submucosal (or Meissner) plexus controls absorption, secretion, and mucosal blood flow. The enteric nervous system is also important in visceral afferent function.

The enteric nervous system develops in utero by migration of neural crest cells to the developing alimentary canal. This migration and the sequence of innervation of different levels of the gut are regulated by specific signaling molecules, which include transcription factors (eg, Mash1), neurotrophic factors (eg, glial-derived neurotrophic factor), and the neuregulin signaling system. These facilitate the growth, differentiation, and persistence of the migrating nerve cells after they arrive in the gut. The receptors for neuregulin proteins are tyrosine kinases, which are important in cell signaling.

Myogenic factors regulate the electrical activity generated by gastrointestinal smooth muscle cells. The interstitial cells of

[a] Portions of this chapter were adapted from Camilleri M. Disorders of gastrointestinal motility. In: Goldman L, Ausiello D, editors. Cecil textbook of medicine, 22nd ed. Philadelphia (PA): WB Saunders; c2004. p. 800-6. Used with permission.

[b] G. Richard Locke III, MD, is gratefully acknowledged as an author of this chapter in a previous edition (parts of which appear in this edition).

Abbreviations: 5-HT, serotonin; TPN, total parenteral nutrition

Cajal, located at the interface of the circular and longitudinal muscle layers of the small intestine, form a nonneural pacemaker system and function as intermediaries between the neurogenic (enteric nervous system) and myogenic control systems. The interstitial cells of Cajal are near the gastrointestinal smooth muscle cells. Electrical control activity spreads through the contiguous segments of the gut through neurochemical activation by excitatory (eg, acetylcholine and substance P) and inhibitory (eg, nitric oxide, somatostatin, and vasoactive intestinal peptide) transmitters.

Gastric and Small-Bowel Motility

The motor functions of the stomach and small intestine are characterized by distinct manometric patterns of activity in the fasting and postprandial periods (Figure 7.1). The fasting (or interdigestive) period is characterized by a cyclic motor phenomenon called the *interdigestive migrating motor complex*. In healthy persons, 1 cycle of the interdigestive migrating motor complex is completed every 60 to 90 minutes, although it may occur much less frequently. The 3 phases of the interdigestive migrating motor complex are a period of quiescence (phase I), a period of intermittent pressure activity (phase II), and an activity front (phase III), during which the stomach and small intestine contract at a frequency that is maximal for each site: 3 per minute in the stomach and 12 per minute in the upper small intestine. The phase III activity front migrates for a variable distance through the small intestine; there is a gradient in the frequency of contractions from approximately 12 per minute in the duodenum to approximately 8 per minute in the ileum. Another characteristic interdigestive motor pattern in the distal small intestine is the *giant migrating complex*, or power contraction; it serves to empty residue from the ileum into the colon in bolus transfers.

In the postprandial period, the interdigestive migrating motor complex is replaced by an irregular pressure response pattern of variable amplitude and frequency, which enables mixing and absorption. This pattern is observed in the regions in contact with food. The maximal frequency of contractions is lower than that noted during phase III of the interdigestive migrating motor complex. The duration of the postprandial motor activity is proportional to the number of calories consumed during the meal: approximately 1 hour for every 200 kcal ingested. Segments of the small intestine that are not in contact with food continue to display interdigestive motor patterns.

The proximal stomach accommodates food through a decrease in its tone, facilitating the ingestion of food without an increase in pressure. This reflex is mediated by the vagus nerve and involves an intrinsic neuronal network that inhibits contractions (eg, nitrergic neurons).

Liquids empty from the stomach in an exponential manner (Figure 7.2). The gastric emptying half-time for nonnutrient liquids in healthy persons is usually less than 20 minutes. Solids are retained selectively in the stomach until particles have been triturated to less than 2 mm in diameter. Therefore, gastric emptying of solids is characterized by an initial lag period followed by a linear postlag emptying phase. The small intestine transports solids and liquids at approximately the same rate. Because of the lag phase for the transport of solids from the stomach, liquids typically arrive in the colon before solids do. Chyme moves from the ileum to the colon intermittently in boluses (Figure 7.2). The movement of gas in the intestines results from fluctuations in intestinal tone and capacitance that produce pressure gradients.

Pathogenesis of Motility Disorders

Gastrointestinal motility disturbances (Table 7.1) result from disorders of the extrinsic or enteric nervous system, interstitial cells of Cajal (or intestinal pacemakers), or smooth muscle. Combined disorders affecting both nerves and muscles occur in systemic sclerosis, amyloidosis, and mitochondrial cytopathy and can appear initially with neuropathic patterns; later, with disease progression, they can display myopathic characteristics, which represent a more advanced stage—often an end stage—of the

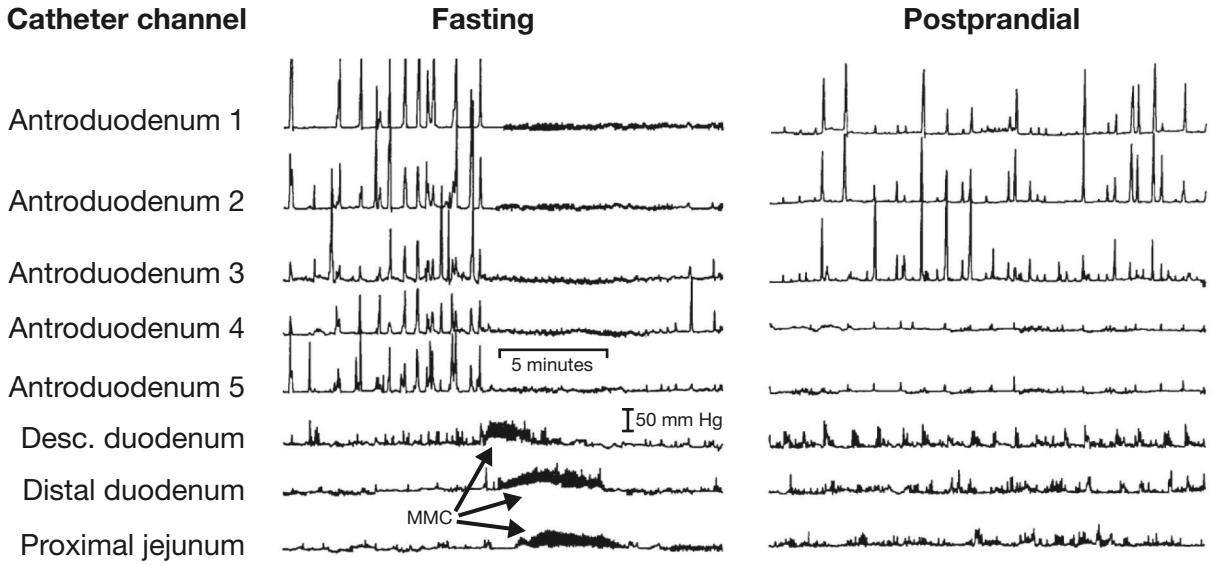

Figure 7.1. Fasting and Postprandial Gastroduodenal Manometric Recordings From a Healthy Volunteer. The volunteer ingested a 535-kcal meal during the study. Note the cyclic interdigestive migrating motor complex (MMC) (left) and the sustained, high-amplitude but irregular pressure activity after the meal (right). Desc. indicates descending. (Adapted from Coulie B, Camilleri M. Intestinal pseudo-obstruction. Annu Rev Med. 1999;50:37-55. Used with permission.)

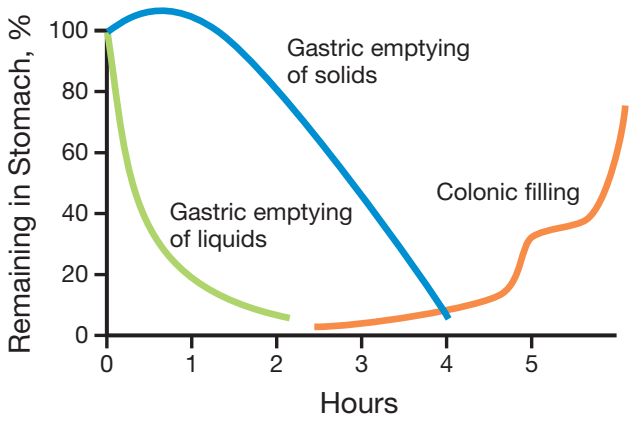

Figure 7.2. Schematic Representation of Typical Gastric Emptying and Colonic Filling Curves. Note the exponential emptying of liquids, in contrast to the initial retention of solids (lag phase), which is followed by a generally linear post-lag emptying rate. The colonic filling curve is characterized by intermittent bolus transfers.

disease. Motility disorders can be congenital (affecting the development of the motility apparatus) or acquired.

Embryologic Processes: Ontogeny of the Gut Neuromuscular Apparatus

Genetic defects in migration, differentiation, and survival of enteric neurons have been identified in several causes of gut dysmotility, including abnormalities of *cRET* (the gene that encodes for the tyrosine kinase receptor), the endothelin B system (which tends to retard development of neural elements, thereby facilitating colonization of the entire gut from the neural crest as primitive neural elements enter through the proximal and distal segments of the developing gut and migrate in oral and anal directions, respectively, to innervate the entire gut), Sox10 (a transcription factor that enhances the maturation of neural precursors), and c-kit (a marker for the interstitial cells of Cajal). Disturbances in these mechanisms result in syndromic dysmotilities such as Hirschsprung disease, Waardenburg-Shah syndrome (pigmentary defects, piebaldism, neural deafness, and megacolon), and idiopathic hypertrophic pyloric stenosis.

Extrinsic Neuropathic Disorders

Extrinsic neuropathic processes include vagotomy, diabetes mellitus, trauma, Parkinson disease, amyloidosis, and a paraneoplastic syndrome usually associated with small cell carcinoma of the lung. Another common "neuropathic" problem met in clinical practice results from the effect of medications such as α_2-adrenergic agonists and anticholinergic agents on neural control.

Damage to the autonomic nerves by trauma, infection, neuropathy, or neurodegeneration may lead to motor, secretory, and sensory disturbances, most frequently resulting in constipation rather than upper gastrointestinal tract motility disorders. Parkinson disease and multiple sclerosis are 2 neurologic diseases involving the extrinsic nervous system that frequently are associated with constipation. In Parkinson disease, there is a decrease in the number of dopamine-containing neurons and the presence of Lewy bodies in myenteric plexus neurons. Also, failure of the striated muscles of the pelvic floor to relax may be an extrapyramidal manifestation of Parkinson disease that aggravates the disturbance of colonic emptying and contributes to the common symptom of constipation. Multiple sclerosis is associated with slow colonic transit and absence of the postprandial motor contractile response in the colon. Gastroparesis and pseudo-obstruction are less frequent than constipation in these 2 diseases.

Table 7.1. Classification of Gastroparesis and Pseudo-obstruction

Type	*Neuropathic*	*Myopathic*
Infiltrative	Progressive systemic sclerosis Amyloidosis	Progressive systemic sclerosis Amyloidosis Systemic lupus erythematosus Ehlers-Danlos syndrome Dermatomyositis
Familial	Familial visceral neuropathies	Familial visceral myopathies Metabolic myopathies
Idiopathic	Idiopathic intestinal pseudo-obstruction	Sporadic hollow visceral myopathy
Neurologic	Porphyria Heavy-metal poisoning Brainstem tumor Parkinson disease Multiple sclerosis Spinal cord transection	Myotonia Other dystrophies
Infectious	Chagas disease Cytomegalovirus Norwalk virus Epstein-Barr virus	
Drug-induced	Tricyclic antidepressants Narcotic agents Anticholinergic agents Antihypertensive agents Antipsychotics Vincristine Laxatives	
Paraneoplastic	Small cell lung carcinoma Carcinoid syndrome	
Postoperative	Postvagotomy with or without pyloroplasty or gastric resection	
Endocrine	Diabetes mellitus Hypothyroidism or hyperthyroidism Hyperparathyroidism	

A broad spectrum of gastrointestinal motility disorders may be related to diabetes mellitus: gastroparesis, pylorospasm, intestinal pseudo-obstruction, diarrhea, constipation, and fecal incontinence. All these manifestations may be caused by autonomic dysfunction (Table 7.2), although evidence points to the importance of acute changes in glycemia (blood glucose >250 mg/dL) and, more importantly, to changes in the structure and function of the enteric nervous system or the interstitial cells of Cajal. From a population perspective, constipation is the most important gastrointestinal symptom in patients with diabetes because it is the most prevalent symptom. Moreover, in a large group that had screening tests for autonomic neuropathy, the prevalence of constipation was 22% among the diabetic patients with neuropathy but only 9.2% among those without neuropathy, which was not significantly different from that of the healthy control group. In a questionnaire-based study of diabetic patients in the community, constipation was more prevalent in patients with insulin-dependent diabetes mellitus than in patients with noninsulin-dependent diabetes mellitus and was associated with symptoms of dysautonomia and the use

Table 7.2. Gastrointestinal (GI) Manifestations of Diabetes Mellitus

GI Manifestation	*Associated Disease*	*Clinical Presentation*
↓ Gallbladder motility		Gallstones
Antral hypomotility		Gastric stasis
Pylorospasm		Bezoars
↓ α_2-Adrenergic tone in enterocytes		Diarrhea, steatorrhea
SB dysmotility	SB bacterial overgrowth	Gastric or SB stasis or rapid SB transit
Colonic dysmotility	Bile acid malabsorption	Constipation or diarrhea
Anorectal dysfunction		Diarrhea or fecal incontinence
Sensory neuropathy		
IAS-sympathetic neuropathy		
EAS-pudendal neuropathy		

Abbreviations: EAS, external anal sphincter; IAS, internal anal sphincter; SB, small-bowel.
Adapted from Camilleri M. Gastrointestinal problems in diabetes. Endocrinol Metab Clin North Am. 1996 Jun;25(2):361-78. Used with permission.

of constipating drugs (eg, calcium channel blockers). In hospital practice, gastroparesis frequently is encountered as a complication of diabetes. Apart from added attention needed for metabolic control, its management follows that of other causes of gastroparesis and pseudo-obstruction. Patients with diabetic gastroparesis (ie, symptoms and objective delay in gastric emptying) require more hospitalizations and physician visits and have higher morbidity and mortality than controls.

Enteric or Intrinsic Neuropathic Disorders

Disorders of the enteric nervous system are usually the result of a degenerative, immune, or inflammatory process. Only rarely can the cause be ascertained in these disturbances. Virally induced gastroparesis (eg, *Rotavirus*, Norwalk virus, cytomegalovirus, or Epstein-Barr virus) and pseudo-obstruction as well as degenerative disorders associated with infiltration of the myenteric plexus by inflammatory cells suggest that infection may be an important predisposing factor. In idiopathic chronic intestinal pseudo-obstruction, there is no disturbance of extrinsic neural control and no identified cause for abnormality of the enteric nervous system.

A full-thickness biopsy specimen from the intestine may be required to evaluate the myenteric plexus and interstitial cells of Cajal. The decision to perform a biopsy needs to be weighed against the risk of complications, including the subsequent formation of adhesions and, possibly, mechanical obstruction superimposed on episodes of pseudo-obstruction.

Smooth Muscle Disorders

Disturbances of smooth muscle may result in major disorders of gastric emptying and small-bowel and colonic transit. These disturbances include systemic sclerosis and amyloidosis. Dermatomyositis, dystrophia myotonica, and metabolic muscle disorders such as mitochondrial cytopathy are seen infrequently. Abnormal facial and external ocular muscle functions may be useful clinical signs of these diseases. In rare instances, there is a positive family history (eg, hollow visceral myopathy may occur either sporadically or in families). Patients with more subtle motility disturbances often present with constipation as a result of metabolic disorders such as hypothyroidism or hyperparathyroidism.

Scleroderma may result in focal or general dilatation, diverticula (often wide-mouthed, especially in the colon), and delayed transit at the levels affected. The amplitude of contractions is decreased (average <30 mm Hg in the distal esophagus, <40 mm Hg in the antrum, and <10 mm Hg in the small bowel) compared with that of controls. Bacterial overgrowth is common and may result in steatorrhea, and it is more likely to occur in myopathic disorders, often with concomitant dilation or diverticula of the small intestine.

A mitochondrial disorder that affects the gut is called *mitochondrial neurogastrointestinal encephalomyopathy*. It is referred to also as oculogastrointestinal muscular dystrophy or familial visceral myopathy type II and is an example of a spectrum of diseases that affect oxidative phosphorylation. It is an autosomal recessive condition with gastrointestinal and liver manifestations that may occur at any age, typically with hepatomegaly or liver failure in the neonate, seizures or diarrhea in infancy, and liver failure or chronic intestinal pseudo-obstruction in children and adults.

Mitochondrial neurogastrointestinal encephalomyopathy is characterized also by external ophthalmoplegia, ptosis, peripheral neuropathy, and leukoencephalopathy. The small intestine is dilated or has multiple diverticula, and the amplitude of contractions is low, typical of a myopathic disorder. Some patients have a combination of intestinal dysmotility or transfer dysphagia due to abnormal coordination and propagation of the swallow through the pharynx and the skeletal muscle portion of the esophagus. This becomes even more devastating when the smooth muscle portion of the esophagus is also affected by the cytopathy.

Management of Gastroparesis and Pseudo-obstruction

Clinical Features

The clinical features of gastroparesis and chronic intestinal pseudo-obstruction are similar and include nausea, vomiting, early satiety, abdominal discomfort, distention, bloating, and anorexia. Patients with severe stasis and vomiting may have considerable weight loss and depletion of mineral and vitamin stores. The severity of the motility problem often manifests itself most clearly in the degree of nutritional and electrolyte depletion. Disturbances of bowel movements, such as diarrhea and constipation, indicate that the motility disorder is more extensive than gastroparesis. Severe vomiting may be complicated by aspiration pneumonia or Mallory-Weiss tears that may result in gastrointestinal tract hemorrhage. When patients have a more generalized motility disorder, they also may have symptoms referable to abnormal swallowing or delayed colonic transit.

A family history and medication history are essential for identifying underlying etiologic factors. A careful review of systems helps reveal an underlying collagen vascular disease (eg, scleroderma) or disturbances of extrinsic neural control that also may be affecting the abdominal viscera. Such symptoms include orthostatic dizziness, difficulties with erection or ejaculation, recurrent urinary tract infections, difficulty with visual accommodation, absence of sweating, and dry mouth, eyes, or vagina.

A succession splash detected on physical examination usually indicates a region of stasis within the gastrointestinal tract, typically the stomach. The hands and mouth may show signs of Raynaud phenomenon or scleroderma. Testing pupillary responses to light and accommodation, testing external ocular

movement, measuring blood pressure in the supine and standing positions, and noting the general features of peripheral neuropathy can identify patients who have a neurologic disturbance or oculogastrointestinal dystrophy associated typically with mitochondrial cytopathy.

Conditions to be differentiated are mechanical obstruction (eg, from peptic stricture or Crohn disease in the small intestine), functional gastrointestinal disorders, and eating disorders such as anorexia nervosa and rumination syndrome. The degree of impairment of gastric emptying in eating disorders is relatively minor compared with that of diabetic or postvagotomy gastric stasis.

A typical history of a person with rumination syndrome is early (0-30 minutes) postprandial, effortless regurgitation of undigested food that happens with virtually every meal. Nausea is typically absent. This condition occurs in mentally challenged children (eg, Down syndrome) but increasingly is recognized in adolescents and adults of normal intelligence. It is treatable with behavioral modification, including diaphragmatic breathing.

Investigation

A motility disorder of the stomach or small bowel should be suspected whenever large volumes are aspirated from the stomach, particularly after an overnight fast or when undigested solid food or large volumes of liquids are observed during esophagogastroduodenoscopy. The following 4 questions should be considered in the management of each patient:

1. Are the symptoms acute or chronic?
2. Is the disease due to neuropathy or myopathy?
3. What regions of the digestive tract are affected?
4. What is the status of hydration and nutrition?

The recommended sequence of investigations is as follows:

1. Suspect and exclude mechanical obstruction. In patients with pseudo-obstruction, plain radiographs of the abdomen taken at the time of symptoms typically show dilated loops of small bowel with associated air-fluid levels. Mechanical obstruction should be excluded with upper gastrointestinal endoscopy and barium studies, including a small-bowel follow-through series or computed tomographic enterography. Imaging studies fortuitously may suggest the presence of a motor disorder, particularly if there is gross dilatation, dilution of barium, or retained solid food within the stomach. However, these studies rarely identify the cause. An exception is small-bowel systemic sclerosis, which is characterized by megaduodenum and packed valvulae conniventes in the small intestine resulting in the "hidebound" radiographic sign.
2. Assess gastric and small-bowel motility. After mechanical obstruction and alternative diagnoses such as Crohn disease have been excluded, a transit profile of the stomach or small bowel (or both) should be performed. For evaluating efficiency in the emptying of solids, scintigraphy offers the most sensitive measurement of upper gastrointestinal tract transit. Scans typically are performed at 0, 1, 2, 4, and 6 hours after ingestion of a radiolabeled meal. Normal values and performance characteristics for the gastric emptying test have been thoroughly described. Alternatives to measuring transit include use of the stable isotope breath test and the wireless motility capsule, but these tests are not as fully validated as scintigraphic gastric emptying. If the cause of the motility disturbance is obvious, such as gastroparesis in a patient with long-standing diabetes mellitus, further diagnostic testing usually is not needed. If the cause is unclear, gastroduodenal manometry, with the use of a multilumen tube with sensors in the distal stomach and proximal small intestine, can distinguish between neuropathic and myopathic processes (Figure 7.3). Neuropathies are characterized by contractions with normal amplitude but with abnormal patterns of contractility. In contrast, the predominant disturbance in myopathic disorders is the low average amplitude of contractions in the segments affected (<40 mm Hg in the antrum, <10 mm Hg in the small intestine) (Figure 7.3).
3. Identify the pathogenesis. Causes of gastroparesis and intestinal pseudo-obstruction are outlined in Table 7.1. In the absence of a cause for a neuropathic pattern of motor activity in the small intestine, it is necessary to pursue additional investigations, including testing for autonomic dysfunction, antineuronal nuclear autoantibodies type 1 associated with paraneoplastic syndromes, and

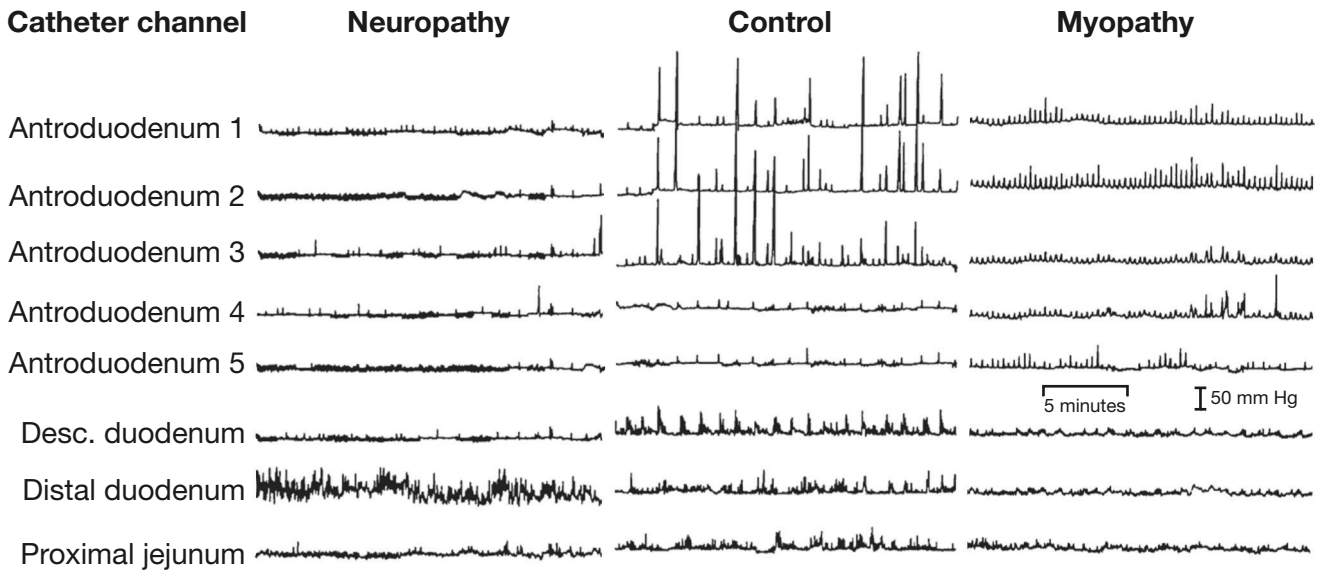

Figure 7.3. Gastroduodenal Manometric Profiles. Postprandial manometric profiles in small-bowel dysmotility due to neuropathy (diabetes mellitus, left) and myopathy (systemic sclerosis, right). Note the simultaneous, prolonged contractions of low amplitude in myopathy. Although the contraction amplitudes are normal in neuropathy, contractile activity is uncoordinated and contractile frequency is decreased. Desc. indicates descending. (Adapted from Coulie B, Camilleri M. Intestinal pseudo-obstruction. Annu Rev Med. 1999;50:37-55. Used with permission.)

magnetic resonance imaging of the brain to exclude a brainstem lesion in patients with vomiting (Figure 7.4). Autonomic testing may include evaluation for orthostatic hypotension, assessment of supine and standing serum norepinephrine levels, measurement of the heart rate interval change during deep breathing, and plasma pancreatic polypeptide response to modified sham feeding. This testing can identify sympathetic adrenergic or vagal neuropathy.

The identification of a myopathic disorder on initial testing should lead to a search for amyloidosis (immunoglobulin electrophoresis, fat aspirate, or rectal biopsy), systemic sclerosis (Scl-70), and a family history of gastrointestinal motility disorders. Laboratory studies to consider include assessment of thyroid function and levels of antinuclear antibody, lactate, creatine phosphokinase, aldolase, and porphyrins and serologic study for Chagas disease. In certain cases, a laparoscopically obtained full-thickness biopsy specimen from the small intestine may be required. Special staining techniques may be needed to identify metabolic muscle disorders, including mitochondrial myopathy. Genetic testing is available to assess for certain mitochondrial myopathies.

4. Identify complications of the motility disorder: bacterial overgrowth, dehydration, and malnutrition. In patients who present with diarrhea, it is important to assess nutritional status (including essential mineral and vitamin levels) and to exclude bacterial overgrowth by culturing small-bowel aspirates or performing hydrogen breath testing. Bacterial overgrowth is relatively uncommon in neuropathic disorders but is more common in myopathic conditions, such as scleroderma, that are associated more often with bowel dilatation, low-amplitude contractions, or small-bowel diverticula. Bacterial overgrowth may be difficult to detect with culture of small-bowel aspirates; however, breath hydrogen after a glucose or lactulose load is a nonspecific test that should be interpreted with caution and in conjunction with small-bowel transit time because the early breath hydrogen peak may be due to bacterial metabolism of the substrate in the colon resulting from fast small-bowel transit. Often, an empirical trial of antibiotic therapy is used as a surrogate for formal testing.

Treatment of Gastroparesis and Intestinal Pseudo-obstruction

Treatment should be designed for each patient, depending on the findings of the investigation. The principal methods of management include correction of hydration and nutritional deficiencies, use of prokinetic and antiemetic medications, suppression of bacterial overgrowth, decompression, and surgical treatment.

Correction of Hydration and Nutritional Deficiencies

Rehydration, electrolyte repletion, and nutritional supplementation are particularly important during acute exacerbations of gastroparesis and chronic intestinal pseudo-obstruction. Restoration of nutrition can be achieved orally, enterally, or parenterally, depending on the severity of the clinical syndrome. Initial nutritional measures include low fiber supplements with the addition of iron, folate, calcium, and vitamins D, K, and B_{12}. Patients with more severe symptoms may require enteral or parenteral supplementation of nutrition. If it is anticipated that enteral supplementation may be required for more than 3 months, it is usually best to provide feedings through a jejunostomy tube. Gastrostomy tubes should be avoided in gastroparesis except for venting purposes.

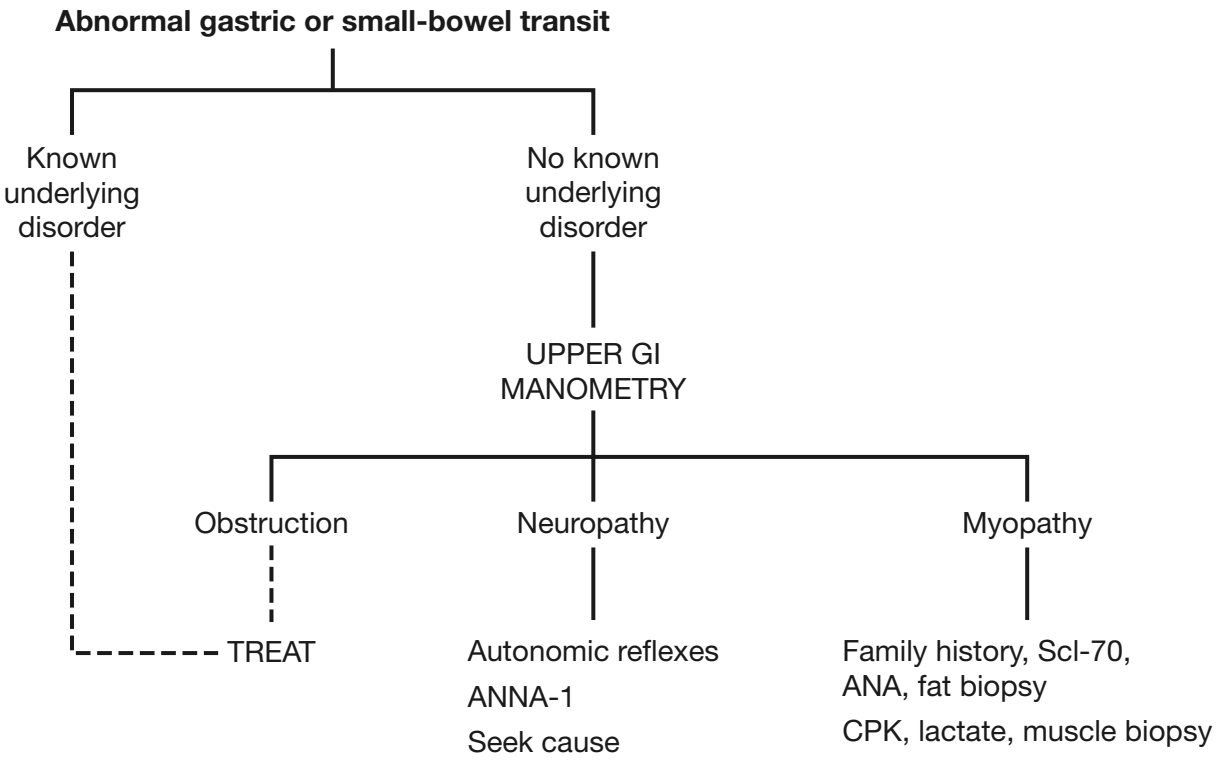

Figure 7.4. Flow Diagram of Steps in Diagnosis of Gastroparesis and Intestinal Pseudo-obstruction. ANA indicates antinuclear antibodies; ANNA-1, antineuronal nuclear antibodies type 1; CPK, creatine phosphokinase; GI, gastrointestinal. (Adapted from Camilleri M, Prather CM. Gastric motor physiology and motor disorders. In: Feldman M, Sleisenger MH, Scharschmidt BF, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. 6th ed. Vol 1, Chap 37, Philadelphia [PA]: Saunders; c1998. p. 572-86. Used with permission.)

Many patients who require long-term parenteral nutrition continue to tolerate some oral feeding.

Medications

Medications may be used to treat neuromuscular motility disorders. However, there is little evidence that they are effective in myopathic disturbances, except for the rare case of dystrophia myotonica affecting the stomach and for small-bowel systemic sclerosis.

Erythromycin, a macrolide antibiotic that stimulates motilin receptors at higher doses (eg, 250-500 mg) and cholinergic mechanisms at lower doses (eg, 40-80 mg), results in the dumping of solids from the stomach. It has been shown to accelerate gastric emptying in gastroparesis; it also increases the amplitude of antral contractions and improves antroduodenal coordination. Erythromycin is most effective when it is given intravenously during acute exacerbations of gastroparesis or intestinal pseudo-obstruction. The usual dose of intravenous erythromycin lactobionate is 3 mg/kg infused over 45 minutes every 8 hours. The efficacy of oral erythromycin appears to be restricted by tolerance and gastrointestinal adverse effects, which often prevent treatment for longer than 1 month; sometimes a low dosage of liquid formula erythromycin (eg, 40-80 mg 3 times daily before meals) can be tolerated. The elixir formulation may improve absorption if the patient has dysmotility. Although studies demonstrated that 2 weeks of treatment was effective for patients with diabetic gastroparesis, there is little evidence that continued therapy produces long-term improvement in gastric emptying or associated symptoms.

Metoclopramide is a dopamine antagonist that has both prokinetic and antiemetic properties. Antiemetic effects are due partly to its antiserotoninergic$_3$ antagonist actions. Long-term use of metoclopramide is limited by the adverse effects of tremor and Parkinson-like symptoms, a consequence of antidopaminergic activity in the central nervous system. Occasionally, tardive dyskinesia occurs. This led to a recommendation that metoclopramide not be given for longer than 3 months (the US Food and Drug Administration ordered a black box warning). It is available in tablet or elixir form and typically is taken 30 minutes before meals and at bedtime. Usual dosages range from 5 to 20 mg 4 times daily, but the drug is safest when the total daily dose is restricted to a maximum of 30 mg.

Serotoninergic (5-HT) agents may prove to be beneficial in the treatment of gastroparesis and intestinal pseudo-obstruction. The combined 5-HT$_4$ agonist and 5-HT$_3$ antagonist, cisapride, was essentially the only medication for which there was evidence for medium- and long-term efficacy; however, the medication is no longer available for prescription because of the risks of cardiac dysrhythmias (torsades de pointes). Newer, more selective 5-HT$_4$ agonists are still experimental, including prucalopride, velusetrag, and naronapride. Other experimental prokinetics are the ghrelin agonists TZP-101 and RM-131, both administered subcutaneously.

Octreotide, a cyclized analogue of somatostatin, has been shown to induce activity fronts in the small intestine that mimic phase III activity of the interdigestive migrating motor complex. Activity fronts in the small bowel are characterized by a simultaneous or very rapidly propagated activity front that is not well coordinated. The clinical effects of octreotide include an initial acceleration of gastric emptying, a decrease in postprandial gastric motility, and inhibition of small-bowel transit. The therapeutic efficacy of octreotide in intestinal dysmotility associated with gastroparesis and pseudo-obstruction has not been demonstrated in clinical trials. Currently, octreotide administered before meals appears to be more useful in the treatment of dumping syndromes associated with accelerated transit. However, it may be useful just before bedtime to induce activity of the migrating motor complex and to propel residue toward the colon with the hope of avoiding bacterial overgrowth. If required during the daytime, octreotide is often given in combination with oral erythromycin to "normalize" the gastric emptying rate.

Antiemetics, including diphenhydramine, prochlorperazine, and metoclopramide, are important in the management of nausea and vomiting in patients with gastroparesis and intestinal pseudo-obstruction. The more expensive 5-HT$_3$ antagonists (eg, ondansetron) have not proved to have greater benefit than the less expensive alternatives.

Antibiotic therapy is indicated for patients who have documented symptomatic bacterial overgrowth (typically manifested as diarrhea and steatorrhea). Although formal clinical trials have not been conducted, it is common practice to use different antibiotics for 7 to 10 days each month in an attempt to avoid development of resistance. Common antibiotics include doxycycline (100 mg twice daily), metronidazole (500 mg 3 times daily), ciprofloxacin (500 mg twice daily), and double-strength trimethoprim-sulfamethoxazole (2 tablets twice daily). Antibiotic therapy for patients with diarrhea and fat malabsorption due to bacterial overgrowth produces considerable symptomatic relief.

Decompression

Decompression is rarely necessary in patients with chronic pseudo-obstruction. However, venting enterostomy (or jejunostomy) is effective in relieving abdominal distention and bloating. It has been shown to decrease significantly the frequency of nasogastric intubations and hospitalizations for acute exacerbations of severe intestinal pseudo-obstruction in patients requiring central parenteral nutrition. Access to the small intestine by enterostomy also provides a way to deliver nutrients enterally and should be considered for patients with intermittent symptoms. The currently available enteral tubes allow for aspiration and feeding by a single apparatus. However, because venting can lead to displacement, some patients need a feeding tube in the jejunum and a venting tube in the stomach.

Surgical Treatment

Surgical treatment has a limited role in patients with gastroparesis and intestinal pseudo-obstruction. For patients who have had multiple abdominal operations, it becomes difficult to discern whether exacerbations of symptoms reflect an underlying disease or adhesions and mechanical obstruction. Surgical treatment should be considered whenever the motility disorder is localized to a resectable portion of the gut. Three instances in which to consider this approach include 1) duodenojejunostomy or duodenoplasty for patients with megaduodenum or duodenal atresia in children, 2) completion gastrectomy for patients with postgastric surgical stasis syndrome, and 3) colectomy with ileorectostomy for intractable constipation associated with chronic colonic pseudo-obstruction.

Novel Therapies

Preliminary data suggest that gastric pacing may improve gastric emptying and symptoms in patients with severe gastroparesis. In humans, gastric pacing has not been able to entrain gastric slow waves to normalize gastric dysrhythmias or to accelerate gastric

emptying. Gastric electrical stimulation is an approved treatment, but data on efficacy are inconclusive and additional controlled clinical trials are needed to assess the long-term benefits, complications, and optimal selection of patients for this treatment.

Currently, small-bowel transplant is limited to patients with intestinal failure who have reversible total parenteral nutrition (TPN)-induced liver disease or life-threatening or recurrent catheter-related sepsis. Combined small-bowel and liver transplant is performed in patients with irreversible TPN-induced liver disease. Complications following small-bowel transplant include infection, rejection, and lymphoproliferative disorders due to long-term immunosuppression and Epstein-Barr virus infection. Studies have suggested that small-bowel transplant may improve quality of life and may be more cost-effective than long-term TPN. Improvements in immunosuppressive regimens, earlier detection of rejection, and treatment of cytomegalovirus infection have enhanced outcomes of small-bowel transplant for short bowel syndrome or severe pseudo-obstruction uncontrolled by TPN. In the meantime, parenteral nutrition is the treatment of choice for most patients.

Functional Dyspepsia

Symptoms of dyspepsia such as epigastric pain or discomfort, nausea, vomiting, early satiety, postprandial fullness, and upper abdominal bloating are encountered commonly in clinical practice. Other chapters of this book review the role of gastroesophageal reflux, peptic ulcer disease, gastritis, and cancer in causing these symptoms. In some parts of the United States and in other countries with a high community prevalence of *Helicobacter pylori* infection, a test-and-treat approach for this infection is indicated and may be effective in relieving functional dyspepsia. Yet, many patients still have symptoms after testing and eradication of *H pylori* and a trial of acid inhibition, usually with a proton pump inhibitor. These patients then undergo upper endoscopy, which usually produces negative findings—that is, no ulcer, esophagitis, or cancer is found. When the symptoms last longer than 3 months, the diagnosis of functional dyspepsia can be made. Multiple potential mechanisms have been postulated for functional dyspepsia (Table 7.3). Similarly, many different therapies have been tried. This multitude of diagnostic and therapeutic options underscores the fact that the cause of functional dyspepsia is not uniform, and hence treatment must be tailored to the identified disorder of function.

Definition

Dyspepsia is not a condition: It is a symptom complex. *Dyspepsia* can be defined as persistent or recurrent abdominal pain or abdominal discomfort centered in the upper abdomen. The term *discomfort* includes symptoms of nausea, vomiting, early satiety, postprandial fullness, and upper abdominal bloating. Symptoms typically are associated with eating but not with bowel movements. The symptoms of heartburn and acid regurgitation are often included as symptoms of dyspepsia; yet, if they are the main symptoms, the patient should be considered to have gastroesophageal reflux rather than dyspepsia. Patients with symptoms or signs typical for biliary tract or pancreatic disease should not be considered to have functional dyspepsia. Thus, right upper quadrant pain or epigastric pain that radiates to the back should not be included in the definition of dyspepsia.

Functional dyspepsia can be defined as dyspepsia symptoms of more than 3 months' duration without an anatomical or biochemical abnormality. Typically, this means negative findings on blood tests and a negative evaluation of the upper gastrointestinal tract with either endoscopy or barium radiography. However, defining endoscopy as "negative" can be difficult. Does this include biopsy study of the esophagus for esophagitis or biopsy study of the stomach for gastritis or *H pylori* infection? Are erythema, erosions, and histologic inflammation meaningful findings? These issues are somewhat controversial.

Surveys have evaluated how many people in the community experience symptoms of dyspepsia. The rates vary in large part because of the definitions used. Some surveys include the symptom of heartburn in the definition of *dyspepsia* and report a prevalence rate of 40%. Other surveys exclude subjects with symptoms of heartburn or irritable bowel syndrome and report prevalence rates of less than 5%. Nonetheless, it is reasonable to state that 15% (about 1 in 7) of the adult population has dyspepsia. Not all these people with dyspepsia have functional dyspepsia. In 1 study, a random sample of the population with dyspepsia underwent endoscopy and only 53% had normal endoscopic findings. The remarkable findings were esophagitis, peptic ulcer disease, duodenitis, and duodenogastric reflux. Of note, only 66% of the asymptomatic controls in this study had normal endoscopic findings! Peptic ulcer disease and duodenitis were more common in the subjects with dyspepsia than in the controls. Other findings such as gastritis were found in a similar number of cases and controls.

Pathophysiology

The most frequently mentioned etiologic possibilities for functional dyspepsia are listed in Table 7.3. The possible causes have been divided into 2 camps: acid or *H pylori* vs motility or sensitivity. The most recent diagnostic criteria for functional dyspepsia (Rome III diagnostic criteria) introduced the terms *epigastric pain syndrome* and *postprandial distress syndrome* in an effort to subclassify the condition.

Whether *H pylori* infection causes symptoms in the absence of an ulcer is still debated. The prevalence of *H pylori* infection and gastritis is only slightly more common in patients with dyspepsia. Still, physicians, investigators, and patients have been interested in the idea that the histologic inflammation produces symptoms. In multicenter, placebo-controlled clinical trials, the effect of the eradication of *H pylori* on functional dyspepsia has been small.

Patients commonly take antacids for relief of dyspepsia; yet, gastric acid secretion is normal in patients with functional dyspepsia. One hypothesis is that patients with functional dyspepsia may be more sensitive to acid. Placebo-controlled trials have shown that acid suppression is modestly more effective than placebo in functional dyspepsia. The question has been whether this is due to occult gastroesophageal reflux that manifests as dyspepsia.

Although clinicians often focus on epigastric pain as the cardinal symptom of functional dyspepsia, most investigators include

Table 7.3. Proposed Causes of Functional Dyspepsia

Acid or Helicobacter pylori	*Motility or Sensitivity*
H pylori infection	Gastroparesis
Gastritis, duodenitis	Abnormal relaxation
Missed peptic ulcer disease	Visceral hypersensitivity
Acid sensitivity	Brain-gut disorder
Occult gastroesophageal reflux disease	Psychologic disorder

other symptoms, such as nausea, fullness, and early satiety. These symptoms suggest that motor abnormalities (delayed or paradoxically accelerated emptying or impaired accommodation) may have a role in causing this condition. Between one-third and one-half of patients with functional dyspepsia who are evaluated in gastrointestinal clinics of referral centers have delayed gastric emptying. Multiple studies, primarily in Europe, have evaluated the role of prokinetics in functional dyspepsia. Generally, prokinetics are 30% more effective than placebo, although the rates varied considerably among studies. Most of these studies were with cisapride or domperidone, neither of which is currently available in the United States. They may be helpful in part because of their antiemetic effects. Treatment with metoclopramide for more than 3 months should be avoided because of the risk of tardive dyskinesia and other adverse effects.

More recently, attention has shifted from gastric emptying to gastric accommodation and gastric sensitivity. Like the heart, the stomach has both systolic and diastolic functions. Recent studies have shown that gastric accommodation (ie, the relaxation of the stomach in response to a meal) is abnormal in patients with functional dyspepsia. Medications such as the anxiolytic buspirone (a 5-HT_{1A} receptor agonist) and the experimental anticholinesterase inhibitor acotiamide appear effective in clinical trials with patients who have functional dyspepsia.

The functional disorders are a continuum of illnesses characterized by gastrointestinal symptoms with negative diagnostic evaluations. There is significant overlap among these disorders. Specifically, at least one-third of patients with functional dyspepsia also have symptoms of irritable bowel syndrome. Patients with irritable bowel syndrome have been shown to have a lower threshold for rectal distention. A similar phenomenon has been noted in functional dyspepsia for distention of the stomach. More recently, imaging of the central nervous system has highlighted the activation of different parts of the brain in subjects with functional gastrointestinal disorders. Thus, the concept of visceral hypersensitivity remains a strong consideration in all the functional gastrointestinal disorders, including functional dyspepsia. Currently, however, no specific medication is available for visceral hypersensitivity, although new agents are being investigated. Clinically, low-dose antidepressants are being prescribed, although there are not any formal clinical trial data.

Recommendations for Evaluation and Therapy

Because of all the controversy from conflicting studies and inadequate data, practice guidelines recommend either a trial of acid inhibition or testing for *H pylori* infection before any diagnostic investigation for dyspepsia. Patients who remain symptomatic need to undergo upper gastrointestinal endoscopy to exclude peptic ulcer disease, esophagitis, and malignancy. After the diagnosis of functional dyspepsia has been made, the first step is to provide reassurance. Some patients with functional dyspepsia want only to be assured that they do not have cancer. They find their symptoms tolerable and require no further intervention. The more difficult decision is whether to perform additional diagnostic testing. The alternative is to proceed directly with empirical trials. Often, the diagnostic tests can be interfaced with therapies such as *H pylori* eradication (if *H pylori* is present), proton pump inhibitors, intermittent use of prokinetics, mucosal protectants such as sucralfate, buspirone, or low-dose antidepressants. Some patients prefer to consider herbal therapy, hypnosis, or cognitive behavioral psychologic therapy.

Summary

Disorders of gastric and small-bowel motility may result in either stasis or accelerated transit. Understanding the mechanisms that control motility and the pathophysiologic mechanisms is the key to optimal management. Simple, quantitative measures of transit and an algorithmic approach to identifying the underlying cause may lead to correction of abnormal function. Correcting dehydration and nutritional abnormalities and providing symptomatic relief are important steps in the management of these patients. Patient education is essential to avoid aggravation of symptoms caused by dietary indiscretions.

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Questions and Answers

Abbreviations used:

ASGE, American Society for Gastrointestinal Endoscopy
CgA, chromogranin A
CMV, cytomegalovirus
EGD, esophagogastroduodenoscopy
FAP, familial adenomatous polyposis
FDA, US Food and Drug Administration
GERD, gastroesophageal reflux disease
H2RA, histamine$_2$-receptor antagonist
HIV, human immunodeficiency virus
HP, *Helicobacter pylori*
MMC, migrating motor complex
NSAID, nonsteroidal antiinflammatory drug
PPI, proton pump inhibitor
PUD, peptic ulcer disease

Multiple Choice (choose the best answer)

II.1. What is the major mechanism responsible for gastrointestinal mucosal damage in patients who use NSAIDs?

a. Excitation of prostaglandin synthesis
b. Inhibition of prostaglandin synthesis
c. Topical or direct damage to the gastrointestinal mucosal surface
d. Direct increase in antral D cell number and level of somatostatin resulting in increased gastric acid secretion
e. Hypertrophy and hyperfunction of parietal cells

II.2. Which of the following medications is contraindicated in the treatment of PUD in a pregnant patient?

a. Ranitidine
b. Sucralfate
c. Misoprostol
d. Pantoprazole
e. Magnesium-containing antacid

II.3. Which of the following patients should *not* be offered therapy for HP infection?

a. HP-infected patients with gastric adenocarcinoma
b. First-degree relatives of HP-infected patients with gastric adenocarcinoma
c. Patients with extranodal marginal zone B-cell lymphoma
d. Pregnant patients during their third trimester of pregnancy
e. HP-infected patients allergic to penicillin

II.4. What is the most cost-effective method of testing for HP infection in a previously untested or untreated patient?

a. Serologic antibody testing
b. Saliva-based antibody testing
c. Urea breath testing
d. Stool antigen
e. Upper endoscopy with gastric biopsies

II.5. Following treatment of HP, which test should *not* be performed to test for eradication of HP?

a. Serologic antibody testing
b. Upper endoscopy with stomach biopsies to check for HP
c. Urea breath test after stopping PPI therapy for 2 weeks
d. Stool antigen
e. Upper endoscopy with urease testing

II.6. Certain environmental factors likely have a role in the development of PUD. Which environmental factor is most associated with PUD?

a. Obesity
b. High intake of red meat
c. Alcohol abuse
d. Cigarette smoking
e. Coffee consumption

II.7. Which of the following is correct regarding pertinent laboratory findings in autoimmune atrophic gastritis?

a. Positive for antiparietal cell antibody, negative for anti–intrinsic factor antibody, high gastrin level, low vitamin B_{12} level
b. Negative for antiparietal cell antibody, positive for anti–intrinsic factor antibody, normal gastrin level, normal vitamin B_{12} level
c. Positive for antiparietal cell antibody, positive for anti–intrinsic factor antibody, high gastrin level, low vitamin B_{12} level
d. Negative for antiparietal cell antibody, negative for anti–intrinsic factor antibody, high gastrin level, low vitamin B_{12} level
e. Positive for antiparietal cell antibody, positive for anti–intrinsic factor antibody, low gastrin level, high vitamin B_{12} level

II.8. Which of the following is a histologic manifestation indicative of present or past HP infection?

a. Adenomatous gastric polyp
b. Lymphocytic gastritis
c. Collagenous gastritis
d. Eosinophilic gastritis
e. Hyperplastic gastric polyp

II.9. A 65-year-old woman presents with complaints of fatigue. Laboratory studies show hemoglobin 10 g/dL, low iron, low ferritin, and elevated total iron-binding capacity. Her colonoscopy is negative and her upper endoscopy shows red linear strips in the antrum. Biopsy was performed. What is the characteristic feature of this condition on biopsy?

a. Fibrin thrombi
b. Moderate to severe inflammation with neutrophilic infiltrate
c. Congestive vasculopathy
d. Superficial lamina propria hemorrhage
e. Moderate inflammation with eosinophilic infiltrate

II.10. A 35-year-old woman presents with epigastric pain, fever, nausea, and vomiting. She has HIV with a CD count less than 200 cells/μL and is not taking any medication for this condition. An upper endoscopy shows antral ulceration. Biopsies are obtained from the ulcer, and the pathologist is able to make a diagnosis. What is the most likely finding on biopsy?

a. Nuclear inclusions with multinucleation, margination, and molding
b. Intense plasma cell infiltration and mononuclear vasculitis
c. Marked lymphoplasmacytic inflammation and neutrophils
d. Vascular endothelial involvement with enlarged cell intranuclear inclusions
e. Positive Warthin-Starry silver staining

II.11. A 45-year-old man presents with mild epigastric pain, nausea, and daily heartburn. On further questioning, he takes ibuprofen twice daily for headaches and he drinks 3 to 4 beers daily. He has been taking omeprazole 20 mg daily for 6 months without any improvement in his symptoms. An upper endoscopy shows only antral erythema with a pool of bile in the gastric body. Biopsies for HP are negative but show marked foveolar hyperplasia and reactive changes. What therapy should you suggest to your patient?

a. Increase the omeprazole dosage to twice daily for 2 months and repeat the upper endoscopy
b. Stop omeprazole and start sucralfate
c. Stop ibuprofen and alcohol
d. Start ursodiol and continue omeprazole at the current dose
e. Start cholestyramine only

II.12. What is the most common cause of granulomatous gastritis?

a. Sarcoidosis
b. Isolated granulomatous gastritis
c. HP gastritis
d. Crohn disease
e. Ulcerative colitis

II.13. A 64-year-old woman presents with flushing, diarrhea, wheezing, and valvular heart disease. If these symptoms represented carcinoid syndrome, what would be the most likely location of the carcinoid tumor?

a. Trachea
b. Stomach
c. Pancreas
d. Jejunum
e. Rectum

II.14. Which of the following is *false* about CgA?

a. CgA is found in various neuroendocrine tissues
b. With its high sensitivity and specificity, measurement of CgA is an excellent screening test for the diagnosis of carcinoid tumor
c. CgA is more sensitive than chromogranins B and C as an indicator of neuroendocrine tumors
d. Blood levels of CgA can be elevated in patients taking an H2RA or a PPI
e. CgA can be used as a tumor marker to assess recurrence after surgical resection

II.15. ASGE guidelines support endoscopic screening or surveillance examinations for gastric cancer in which of the following patient groups?

a. Patients with biopsy-proven hyperplastic or inflammatory gastric polyps
b. Patients whose prior endoscopy demonstrated intestinal metaplasia
c. All patients with pernicious anemia
d. Patients with a previous partial gastrectomy for PUD
e. Patients with FAP

II.16. Which of the following statements about the association between HP and gastric malignancies is *false*?

a. Nearly half of all gastric cancers in developing countries are solely attributable to HP infection
b. HP has been linked to the development of both gastric adenocarcinoma and gastric lymphoma
c. The relative risk of HP gastric infection leading to the subsequent development of gastric adenocarcinoma appears to be greatest among the elderly
d. Gastric cancer develops in only a very small minority of patients infected with HP
e. Most gastric carcinomas associated with HP develop in the distal stomach (body and antrum regions)

II.17. Which of the following is considered a region or nation where the incidence of gastric cancer is *not* high?

a. Eastern Europe
b. Australia
c. Western South America
d. Japan
e. Eastern Asia

II.18. Which of the following is most likely in a patient with a glucagonoma?

a. The tumor is probably unresectable
b. The patient's glucagon level is 200 pg/mL
c. The patient has a fasting blood glucose of about 100 mg/dL
d. The tumor is located in the duodenum
e. The patient is constipated

II.19. Which of the following components of extrinsic neural control promote transit?

a. Activation of parasympathetic outflow to nonsphincteric smooth muscle

b. Activation of thoracolumbar sympathetic outflow to non-sphincteric smooth muscle
c. Inhibition of sacral parasympathetic outflow to sphincters
d. Activation of thoracolumbar sympathetic outflow to sphincters
e. All of the above

II.20. Which of the following is more likely to present as a myopathic disorder of gastrointestinal motility rather than as a neuropathic disorder?

a. Parkinson disease
b. Diabetes mellitus
c. Multiple sclerosis
d. Anticholinergic medication use
e. Dermatomyositis

II.21. A previously healthy 15-year-old high school student is brought to your office by her mother with a 6-month history of vomiting her food after eating. She denies dysphagia or abdominal pain, and she has lost 2.3 kg. Results of standard laboratory tests are normal. Endoscopy showed grade A (Los Angeles classification) distal erosive esophagitis. Acid-lowering medications have not been helpful. Which of the following is likely to be diagnostic?

a. Morning serum cortisol level
b. Esophageal impedance study in the absence of medications
c. HIV testing
d. Psychiatric evaluation
e. Porphyrin analysis

II.22. A 62-year-old woman presents with anorexia, postprandial nausea, belching, and bloating. She has lost 8.2 kg. She denies dysphagia or any change in her bowel habit. She is not diabetic, but she has smoked a pack a day for 45 years. On abdominal examination, while fasting, there is a succession splash. A radiograph of the abdomen shows distention of the stomach, small bowel, and colon. Which of the following is the most likely diagnosis?

a. Small cell lung cancer
b. Functional dyspepsia
c. Colorectal cancer
d. Gastroparesis
e. Irritable bowel syndrome

II.23. Which of the following statements regarding gastric motility is true?

a. Liquids are emptied from the stomach without a lag phase, in a linear manner
b. Indigestible solids are emptied from the stomach by the MMC when they are smaller than 3 cm in diameter
c. Solids are emptied from the stomach after an initial lag phase followed by a linear emptying phase
d. Delayed gastric emptying is a major cause of symptoms in functional dyspepsia
e. During phase III of the MMC, gastric contraction waves occur at a maximum of 3 cycles/s

II.24. Which of the following is *unlikely* to pass through the pylorus?

a. A 26-mm-diameter coin
b. A 40-mm long soft plastic stirring rod
c. A 35-mm meatball swallowed whole
d. A 15-mm sharp straight pin
e. A 15-mm wooden toothpick

Answers

II.1. Answer b.
NSAIDs systemically inhibit the production of prostaglandins and can cause direct damage to the mucosal surface. However, the inhibition of prostaglandin synthesis is the main mechanism of ulcer formation. Chronic antral gastric inflammation as a result of HP infection can decrease the number of antral D cells and level of somatostatin. This change leads to an increased rate of gastric acid secretion and an increased likelihood of duodenal ulcer formation.

II.2. Answer c.
Misoprostol is contraindicated in pregnancy because it increases the risk of major birth defects. Ranitidine, sucralfate, pantoprazole, and most antacids are all considered low risk or FDA pregnancy category B. For medications in category B, either 1) animal studies have not shown a fetal risk, but there are no controlled studies in pregnant women, or 2) animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester of pregnancy.

II.3. Answer d.
Testing for HP should not be conducted if the patient will not be offered treatment. All patients who test positive for HP infection should be treated. Others who should receive treatment are HP-infected patients with gastric adenocarcinoma or extranodal marginal zone B-cell lymphoma (ie, mucosa-associated lymphoid tissue lymphoma [MALToma]) and first-degree relatives of HP-infected patients with gastric adenocarcinoma. Pregnant patients with active HP infections should not be treated until after delivery. Acid suppression is the mainstay of therapy for HP-positive patients during pregnancy.

II.4. Answer a.
Noninvasive testing is less expensive overall because it does not involve the expense of upper endoscopy for invasive testing. Of the available noninvasive tests, laboratory-based serologic testing is more sensitive and specific than office-based tests. The sensitivity of this test is 86% to 94% and the specificity is 78% to 95%. Thus, serologic antibody testing is the most cost-effective method for this type of patient.

II.5. Answer a.
Serologic testing cannot distinguish active HP infection from previous infection. The other tests could determine whether HP infection is persistent. Testing that includes upper endoscopy would be the least cost-effective method of checking for eradication.

II.6. Answer d.
PUD is more common in persons who smoke cigarettes and it is more likely to be complicated. Obesity, red meat intake, alcohol use or abuse, and coffee consumption are not known risk factors for PUD.

II.7. Answer c.
Autoimmune gastritis is an autosomal dominant condition and an uncommon cause of chronic gastritis. Most commonly, patients are white women in their 50s and 60s. It affects the gastric body and fundus. Tests for antibodies to antiparietal cells and anti–intrinsic factor are positive. The loss of parietal cells causes a low acid state, which stimulates gastrin cell hyperplasia.

II.8. Answer b.
HP infection has various histologic manifestations. Acute HP gastritis is rarely seen, but chronic inactive gastritis is commonly found on biopsy. It is also associated with granulomatous gastritis, gastric hyperplastic polyp formation, multifocal atrophic gastritis, and lymphocytic gastritis. When lymphocytic gastritis is found on biopsy, it is important to test for HP and treat if positive.

II.9. Answer a.
The patient's presentation and upper endoscopy findings are consistent with gastric vascular ectasia. The characteristic feature on biopsy is fibrin thrombi. Other expected findings are dilated mucosal capillaries, fibromuscular hyperplasia of the lamina propria, and minimal or absent inflammation. Congestive vasculopathy is found in portal hypertensive gastropathy, superficial lamina propria hemorrhage is found in acute erosive gastritis, and inflammation with eosinophilic infiltrate is found in eosinophilic gastritis. Treatment of gastric vascular ectasia is driven by the rate of blood loss.

II.10. Answer d.
The most likely infection is CMV infection. Biopsies should be obtained from the center of the ulcer as well as from the edges of the ulcer. CMV infections have vascular endothelial involvement with enlarged cell "owl's eye" intranuclear inclusions, so the biopsies from the center of the ulcer will have the highest yield in this infection. In herpes simplex infections, biopsies from the edge of the ulcer will be higher yield and will show nuclear inclusions with multinucleation, margination, and molding. Intense plasma cell infiltration and mononuclear vasculitis are seen with syphilis. A silver stain, such as Warthin-Starry silver stain, is helpful in diagnosing syphilis. Marked lymphoplasmacytic inflammation and neutrophils are seen in the chronic active gastritis form of HP infection.

II.11. Answer c.
This patient's symptoms, upper endoscopy findings, and biopsies are consistent with chemical gastropathy. Common causes include chronic aspirin or NSAID use, alcohol, and bile salts. Given that all 3 offending agents are present in this case, removing at least 2 will likely improve his symptoms. He should stop using NSAIDs and alcohol. Omeprazole can be continued, but there is no need to repeat an upper endoscopy in 2 months. Sucralfate, ursodiol, and cholestyramine are unlikely to be helpful.

II.12. Answer d.
The differential diagnosis of granulomatous gastritis is broad, but the most common cause is gastric Crohn disease. It accounts for 52% of the cases. The next most common cause is isolated granulomatous gastritis (25%).

II.13. Answer d.
Carcinoid syndrome is most frequently associated with tumors of the midgut (small bowel), where the secretory products are directly released into the bloodstream and not metabolized by the liver. Midgut tumors are the most common, and they frequently metastasize to the liver.

II.14. Answer b.
The specificity of CgA levels is relatively low because of day-to-day variation in CgA secretion in healthy patients and in patients with carcinoid tumors. The blood level can also be elevated in patients who have various medical conditions or have ingested certain foods and medications. Therefore, CgA should not be used in isolation as a screening test for carcinoid tumors.

II.15. Answer e.
Use of EGD for gastric cancer screening and surveillance is recommended by the ASGE only for those with FAP, but EGD may need to be considered on an individual basis in many situations, depending on the patient's country of origin, family history, findings on prior endoscopic examinations, and other factors.

II.16. Answer c.
The relative risk of HP gastric infection leading to the subsequent development of gastric adenocarcinoma is greatest among young patients (relative risk is 9.3 for patients younger than 29 years). The absolute risk for young patients is quite low, but it is much greater than the risk for elderly patients.

II.17. Answer b.
Australia is the only nation or region listed where the incidence of gastric cancer is not high.

II.18. Answer a.
Patients with a glucagonoma usually present with a serum glucagon level of more than 1,000 pg/mL and a high fasting blood glucose level (usually >200 mg/dL). The tumor is located almost always in the pancreas, and patients have diarrhea. The tumor is usually unresectable; most patients present with liver metastases and therefore are not candidates for curative surgical resection.

II.19. Answer a.
Cranial and sacral parasympathetic activation is excitatory to nonsphincteric smooth muscle and inhibitory to sphincters, while thoracolumbar sympathetic activation is inhibitory to nonsphincteric smooth muscle and excitatory to sphincters.

II.20. Answer e.
Mitochondrial cytopathies, as well as systemic sclerosis, dermatomyositis, systemic lupus erythematosus, dystrophia, myotonia, and Ehlers-Danlos syndrome can result in myopathic disorders. Amyloidosis, systemic sclerosis, and mitochondrial cytopathy can be neuropathic initially and myopathic later.

II.21. Answer d.
This previously healthy 15-year-old with normal blood test results, minimal weight loss, and mild distal esophagitis may have an eating disorder with functional vomiting or regurgitation. Obtaining further history with psychiatric evaluation is more likely to be diagnostic than testing for porphyria, Addison disease, or HIV. Her mild erosive GERD is likely secondary to her regurgitation or functional vomiting. By history, effortless regurgitation can be distinguished from forceful vomiting.

II.22. Answer a.
This woman has a long history of smoking and most likely has small cell lung cancer with paraneoplastic pseudo-obstruction and hence, gastric, small bowel, and colonic dilatation. Functional dyspepsia and irritable bowel syndrome would not explain her weight loss and diffuse gastrointestinal dilatation. Gastric dilatation with succession splash and no change in bowel habit would not be consistent with an obstructing colorectal cancer. Gastroparesis alone would not explain small bowel and colonic dilatation.

II.23. Answer c.
Liquids empty in an exponential manner (not linear). Indigestible solids must be smaller than 2 cm to exit the stomach during the MMC. Gastric contraction waves during the MMC occur at a maximum of 3 cycles/min, not 3 cycles/s. Answer choice *d* is false.

II.24. Answer a.
Objects larger than 2.0 to 2.5 cm in diameter (answer choice *a*) are unlikely to pass through the pylorus unless the stomach can grind them down to smaller pieces (answer choice *c*). Long, thin objects shorter than 5 to 6 cm (answer choices *b, d*, and *e*) are likely to pass. It would not be prudent to let an object pass into the small bowel, where it could cause injury (answer choices *d* and *e*).

III

Small Bowel and Nutrition

8

Clinical Features of Malabsorptive Disorders, Small-Bowel Diseases, and Bacterial Overgrowth Syndromes

AMY S. OXENTENKO, MD

Malabsorptive Disorders and Diarrhea

Both malabsorption (a defect in the mucosal absorption of nutrients) and maldigestion (a defect in the hydrolysis of nutrients) imply disordered physiologic mechanisms in the gastrointestinal system. Malabsorption and maldigestion of nutritional substrates can occur in multiple phases: 1) the *luminal phase*, in which there is contact between ingested food and various digestive enzymes; 2) the *mucosal phase*, in which substances are assimilated and absorbed in the required constituent form; and 3) the *delivery phase*, in which nutrients are taken up into the cytoplasm and transported to the lymphatics or portal venous system (Table 8.1).

Carbohydrate Malabsorption

Starch, sucrose, and lactose account for nearly 85% of ingested carbohydrates, with starches alone comprising 50%. For starches to be absorbed, they first are digested by salivary α-amylase and pancreatic α-amylase—mainly the latter—into disaccharides and oligosaccharides of maltose, maltotriose, and α-dextrins, which are then hydrolyzed by brush border enzymes to form the monosaccharide glucose. Sucrose is hydrolyzed by sucrase to form glucose and fructose, whereas lactose is hydrolyzed by lactase to form glucose and galactose. After being cleaved by the brush border disaccharidases, these monosaccharides can be absorbed into the cytoplasm. Fructose is transported by facilitated diffusion, but glucose and galactose are transported by sodium–glucose-linked transporter 1 (SGLT-1); oral rehydration solutions are effective because of the inclusion of both sodium and glucose in concentrations that maximize use of this transport system (see below).

Carbohydrate malabsorption can be caused by either a decrease in mucosal surface area (absolute or relative) or a decrease in disaccharidases or transport proteins. Carbohydrates that are not absorbed increase the osmolality within the intestinal lumen, resulting in more fluid being drawn into the lumen to maintain an isosmotic state. Colonic bacterial fermentation of these malabsorbed substances increases intestinal gas. The most common clinical syndrome of carbohydrate malabsorption is from lactase deficiency. Congenital lactase deficiency is present at birth and is rare. Primary lactase deficiency has a delayed onset, with the highest prevalence among Native Americans and people from sub-Saharan Africa and Asia. A secondary, or late-onset, acquired lactase deficiency may occur after intestinal resection, mucosal disease, or a postinfectious syndrome. Because lactase is present on the microvillous surface, it is often the first disaccharidase affected by small-bowel mucosal diseases. Less common conditions associated with disaccharidase deficiencies include sucrase-isomaltase deficiency (an inherited condition) and trehalase deficiency (trehalose is a sugar found in various mushrooms).

The clinical features of carbohydrate malabsorption include odorless flatus, bloating, and osmotic diarrhea. Weight loss should not occur with isolated carbohydrate malabsorption. A detailed dietary history can suggest the disorder. The diagnosis may be supported by the findings of an increased stool osmotic gap (>100 mOsm/kg) and stool pH less than 6 (the pH reflects the release of hydrogen and short-chain fatty acids from carbohydrate fermentation in the colon). The mucosal enzyme activity of the various disaccharidases can be quantified (more often done in pediatric patients), but the procedure is invasive and not widely available. Hydrogen breath tests have largely replaced

Abbreviations: DGP, deaminated gliadin peptide; EATL, enteropathy-associated T-cell lymphoma; EMA, endomysial antibody; PAS, periodic acid-Schiff; PCR, polymerase chain reaction; SGLT-1, sodium–glucose-linked transporter 1; SIBO, small intestinal bacterial overgrowth; tTG, tissue transglutaminase antibody

Table 8.1. Mechanisms of Malabsorption and Maldigestion

Defect	*Cause*	*Examples*
Luminal phase		
Defective fat hydrolysis	Decreased lipase	Pancreatic insufficiency
	Decreased duodenal pH	Zollinger-Ellison syndrome
	Impaired mixing	Postgastrectomy
Defective protein hydrolysis	Decreased proteases	Pancreatic insufficiency
	Absence of enterokinase	Congenital deficiency
Impaired solubilization	Decreased micelle formation	Liver disease
		Biliary obstruction
		Ileal resection or disease
		Drugs (cholestyramine)
	Deconjugation of bile salts	Bacterial overgrowth
Mucosal phase		
Diffuse mucosal damage	Diminished surface area, altered absorption or secretion	Celiac disease, tropical sprue, Crohn disease, Whipple disease, amyloidosis
Decreased brush border enzymes	Congenital or acquired deficiency	Lactase, trehalase, or sucrose deficiencies
	Small-bowel damage	Postinfectious lactase deficiency
Transporter defects	Single enzyme defects	Hartnup disease, cystinuria
Delivery phase		
Lymphatic derangement	Ectasia of lymphatics	Lymphangiectasis
	Increased lymphatic pressure	Congestive heart failure, pericardial constriction, lymphoma, fibrosis

Data from Riley SA, Marsh MN. Maldigestion and malabsorption. In: Feldman M, Scharschmidt BF, Sleisenger MH, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. 6th ed. Vol 2. Philadelphia (PA): Saunders; c1998. p. 1501-22.

oral tolerance tests; an increase in breath hydrogen of at least 20 parts per million above baseline during the 3-hour study is indicative of colonic fermentation of the nonabsorbed carbohydrate by bacteria. False-positive results (small intestinal bacterial overgrowth [SIBO] or inadequate dietary instructions) and false-negative results (recent treatment with antibiotics or non-hydrogen producers) can occur with breath testing. Tolerance to lactose-containing products can be improved if they are ingested with other foods, especially in amounts of less than 15 g (equivalent to about 300 mL of milk).

Fat Malabsorption

Fat malabsorption is a complex process that requires adequate function of the pancreas, liver and biliary system, small-bowel mucosa, and lymphatic system. Triglycerides constitute the majority of dietary fat. Initial lipolytic activity begins in the stomach through the action of gastric lipase, although this contributes little to digestion in most people. Pancreatic lipase has a much larger role in hydrolyzing dietary triglycerides. Because the optimal activity of this enzyme is at a pH of 8, it is inactivated in acid overproduction states (eg, Zollinger-Ellison syndrome and mastocytosis). Pancreatic lipase hydrolyzes dietary triglycerides into free fatty acids and β-monoglycerol. These constituents then combine with conjugated bile salts from the liver to form water-soluble micelles, which allow passage into enterocytes. At the level of the enterocyte, triglycerides are reesterified, synthesized into chylomicrons, and distributed systemically through the lymphatics. Although pancreatic function is required for fat digestion, a person may lose nearly 90% of lipase output from the pancreas before the efficiency of fat digestion and absorption is affected. Unlike long-chain triglycerides, which require bile salts and micelle production for absorption, medium-chain triglycerides do not require micelle formation for absorption and can be absorbed directly into the portal blood. This mechanism can be used to provide triglycerides in the diet without worsening fat malabsorption in patients with bile salt deficiency, such as patients who have had more than 100 cm of distal small bowel resected.

The clinical features of fat malabsorption include diarrhea, weight loss, and complications from deficiencies of fat-soluble vitamins (vitamins A, D, E, and K). Although the amount of fat in the stool can be assessed qualitatively with Sudan staining, this test has relatively low sensitivity and specificity. Quantification of fecal fat excretion is considered the "gold standard" for establishing the presence of fat malabsorption. The normal value for fecal fat excretion is less than 7 g daily, but patients with diarrhea from any cause may have up to 14 g daily before it represents true fat malabsorption. A 72-hour stool collection is optimal; the patient should receive a diet containing 100 g of fat daily for several days before stool collection commences and continue the high-fat diet throughout the stool collection process. The patient should be instructed to avoid antidiarrheal agents or pancreatic enzyme replacement immediately before and during the stool collection so that the stool volume and fat will be accurately reflected.

Once fat malabsorption has been confirmed, the cause needs to be determined. In some cases, the cause may be apparent clinically. The most common clinical conditions result from small-bowel diseases or pancreatic insufficiency. Although D-xylose testing has limited clinical availability, it can help distinguish between a small-bowel and a pancreatic source of fat malabsorption because D-xylose is absorbed normally by the small-bowel mucosa and excreted in the urine. After ingestion of 25 g of D-xylose, a 1-hour serum or a 5-hour urine sample (or both) can be collected. A serum level of D-xylose less than 20 mg/dL per hour or a urine concentration less than 5 g per 5 hours suggests failure of small-bowel absorption. Increased levels of D-xylose in the serum or urine suggest that the small-bowel mucosa is intact, thus indicating pancreatic insufficiency. Many factors can influence the test results, including gastroparesis, vomiting, and inadequate collection of urine. Evaluation for small-bowel abnormalities that can lead to fat malabsorption could include small-bowel biopsies (eg, celiac disease or amyloid), small-bowel cultures, or hydrogen breath testing (eg, SIBO), as well as small-bowel imaging (eg, Crohn

disease or radiation enteritis). To evaluate for pancreatic causes of fat malabsorption, imaging (computed tomography, magnetic resonance cholangiopancreatography, or endoscopic ultrasonography) can be used to examine for changes due to chronic pancreatitis. Calcifications seen in the pancreas on plain films can be helpful, but they are infrequent. Tests of pancreatic function are not widely available but can be performed with secretin (to measure bicarbonate) and cholecystokinin (to measure lipase or trypsin). Alternatively, an empirical trial of pancreatic enzymes can be recommended, with fecal fat quantification before and after the trial to assess objectively for improvement.

Protein Malabsorption

Protein digestion and absorption require adequate pancreatic function and integrity of the intestinal mucosa. Ingested proteins are cleaved initially by pepsin (an endopeptidase), which is produced from the precursor pepsinogen in response to a gastric pH between 1 and 3, with inactivation at a pH greater than 5. When gastric chyme reaches the small intestine, enterokinase from duodenal enterocytes activates trypsin. Trypsin then converts pancreatic proteases from inactive to active forms in a cascade fashion, subsequently cleaving proteins into various amino acids and small peptides. Additional mucosal brush border oligopeptidases further cleave small peptides, with free amino acids and oligopeptides crossing into the cytoplasm either freely or through carrier-mediated channels, some of which are sodium-mediated channels.

In addition to disorders that affect protein digestion and absorption, there can be significant loss of protein from the intestinal tract; these conditions are referred to as *protein-losing enteropathies*. Although the liver can respond to protein loss by increasing the production of various proteins such as albumin, a protein-losing state develops when net loss exceeds net production. Three major categories of gastrointestinal-related disorders are associated with excess protein loss: 1) diseases with increased mucosal permeability without erosions, 2) diseases with mucosal erosions, and 3) diseases with increased lymphatic pressure. Examples of clinical conditions in each of these categories are listed in Box 8.1.

The clinical features of a protein-losing enteropathy include diarrhea, edema, ascites, and possible concomitant carbohydrate and fat malabsorption, because isolated protein malabsorption or loss is infrequent. Laboratory studies may show a low serum level of protein, albumin, and immunoglobulins, except for IgE, which has a short half-life and rapid synthesis. If the protein-losing state is from lymphangiectasia (primary or acquired), patients may also have lymphocytopenia. To diagnose a protein-losing enteropathy, an α_1-antitrypsin clearance test should be performed. α_1-Antitrypsin is unique in that it is neither absorbed nor secreted from the intestinal mucosa, and unlike other proteins, it is resistant to proteolysis (with the exception of pepsin). Therefore, its clearance reflects a true protein-losing state. If a protein-losing gastropathy is suspected (eg, Ménétrier disease), the patient should receive acid-suppressive therapy before an α_1-antitrypsin clearance test is performed. This sequence avoids degradation of α_1-antitrypsin by pepsin, since the elevated pH from acid suppression will inactivate pepsin and hence allow adequate assessment of gastric loss.

Box 8.1. Causes of Protein-Losing Enteropathies

Nonerosive disease
- Ménétrier disease
- *Helicobacter pylori* gastritis
- Eosinophilic gastroenteritis
- Celiac disease
- Small intestinal bacterial overgrowth
- Whipple disease
- Vasculitides

Erosive disease
- Amyloidosis
- Inflammatory bowel disease
- Graft-versus-host disease
- *Clostridium difficile* colitis
- Ischemia

Increased lymphatic pressure
- Congestive heart failure
- Constrictive pericarditis
- Lymphangiectasia (primary vs acquired)
- Lymphatic obstruction (lymphoma)
- Mesenteric venous thrombosis
- Retroperitoneal fibrosis

Adapted from Greenwald DA. Protein-losing gastroenteropathy. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. 9th ed. Vol 1. Philadelphia (PA): Saunders/Elsevier; c2010. p. 437-43. Used with permission.

Diarrhea

The mechanism for diarrhea is often from a combination of decreased absorption (a villous function) and increased secretion (a crypt function). Diarrhea can be categorized in several ways: inflammatory versus noninflammatory and secretory versus osmotic. The clinical features of inflammatory diarrhea may include abdominal pain, fever, and tenesmus. Stools may be mucoid, bloody, smaller volume, and more frequent, unless the small bowel also is affected diffusely. Microscopically, the stools can contain blood and leukocytes. However, if the inflammation is microscopic, these clinical and stool features may be absent (eg, microscopic colitis). Common causes of inflammatory diarrhea include invasive infections, inflammatory bowel disease, radiation enteropathy, and ischemia. Noninflammatory causes of diarrhea tend to produce watery diarrhea, without fever or gross blood, and the stool appears normal on microscopy. There are many causes, but infections, particularly by toxin-producing organisms, are common.

Distinguishing whether diarrhea is osmotic or secretory can be useful clinically. Osmotic diarrhea is due to the ingestion of poorly absorbed cations, anions, sugars, or sugar alcohols (such as sorbitol or xylitol). These ingested ions obligate retention of water in the intestinal lumen to maintain osmolality equal to that of other body fluids (290 mOsm/kg); this subsequently causes diarrhea. Osmotic diarrhea can occur also from maldigestion or malabsorption (pancreatic insufficiency or disaccharidase deficiency). The stool osmotic gap is calculated by adding the stool sodium and potassium concentrations, multiplying by 2, and subtracting this amount from 290 mOsm/kg. A gap greater than 100 mOsm/kg strongly supports an osmotic cause for the diarrhea, whereas a gap less than 50 mOsm/kg supports a secretory cause. Stool osmolality does not necessarily need to be measured because the value should be the same as that of the serum (290 mOsm/kg), with lower values indicating urine or water

contamination and higher values indicating that the specimen was not processed readily. The utility of checking stool osmolality therefore lies in determining whether the stool specimen was processed properly. Stool volumes tend to be less with osmotic diarrhea than with secretory diarrhea, and the diarrhea tends to abate with fasting.

For secretory diarrhea to occur, the primary bowel function converts from net absorption to net secretion. Normally, up to 9 to 10 L of intestinal fluid crosses the ligament of Treitz each day, and all but 1.5 L crosses the ileocecal valve, demonstrating the tremendous absorptive capacity of the small bowel. The colon then absorbs all but 100 to 200 mL of the fluid, which is evacuated as stool. In secretory diarrhea, net absorption converts to net secretion, and the small bowel loses its normal capacity to absorb the large volume of fluid; thus, liters of fluid pass into the colon daily. Although the colon can adapt and absorb nearly 4 L of liquid from the stool each day, larger fluid loads cannot be absorbed, and this results in large-volume diarrhea, often liters per day. Secretory diarrhea does not abate with fasting. Dehydration can occur easily, and replacement fluids need to contain adequate concentrations of both sodium and glucose, as in oral rehydration solutions, to maximize small-bowel absorption of sodium and water. Consuming beverages that have low sodium concentrations (water, sports drinks, or juices) may actually worsen the volume status of the patient because sodium will be secreted into the bowel lumen to maintain an isosmotic state, with water following the stool sodium loss. Sodium and glucose absorption from the small bowel occurs through the transporter SGLT-1. Characteristics, common causes, and testing strategies for secretory and osmotic diarrhea are listed in Table 8.2.

Intestinal Resections and Short Bowel

Diarrhea and malabsorption can result from any process that shortens the length of the functioning small bowel, whether from surgery or from relative shortening caused by underlying disease. Whether diarrhea and malabsorption occur with a shortened small bowel depends on several factors: the length of bowel resected, the location of the bowel resected, the integrity of the remaining bowel, and the presence of the colon. The length and location of the resected small bowel affect the enterohepatic circulation of bile. Typically, bile salts are reabsorbed from the terminal ileum. If *less* than 100 cm of distal ileum is resected, the liver can compensate for the loss of absorptive capacity by producing an increased amount of bile salts, which enter the colon and cause a bile-irritant secretory diarrhea. This diarrhea is treated with cholestyramine, which binds the excess bile salts and improves diarrhea. If *more* than 100 cm of distal small bowel is resected, including the terminal ileum, the liver can no longer compensate for the loss of absorptive capacity. The resulting bile salt deficiency leads to steatorrhea since micelle production is negatively affected and long-chain triglycerides cannot be effectively handled. This can be managed by prescribing a diet that consists of medium-chain triglycerides, which do not require bile salts or micelle formation for absorption because they are absorbed directly into the portal blood.

The location of the small-bowel resection is also important. The terminal ileum has the specialized function of absorbing and recirculating bile salts and binding the cobalamin-intrinsic factor complex. When the jejunum is resected, the ileum assumes all the functions of the jejunum. However, the opposite is not true; the jejunum is not able to compensate for the loss of the

Table 8.2. Comparison of Osmotic and Secretory Diarrhea

	Type of Diarrhea	
Feature	*Osmotic*	*Secretory*
Daily stool volume, L	<1	>1
Effect of fast on diarrhea	Stops	Continues
Stool osmotic gap, mOsm/kg	>100	<50
	Common Causes	
	Disaccharidase deficiency	Infections and toxins
	Lactase	Cholera
	Trehalase	Bile acids
	Sucrase-isomaltase	Microscopic colitis
	Iatrogenic	Neuroendocrine tumors
	Polyethylene glycol solution	Medullary carcinoma of thyroid (calcitonin)
	Lactulose	VIPoma
	Magnesium antacids or supplementation	Gastrin (not pure secretory)
	Sweeteners and elixirs	Carcinoid syndrome
	Sorbitol	Laxatives (nonosmotic)
	Xylitol	Diabetic diarrhea
	Fructose	Transporter defects or deficiencies
		Chloridorrhea
		Idiopathic
	Testing Strategies	
	Dietary review	Stool cultures
	Carbohydrate malabsorption	Structural or mucosal evaluation
	Breath testing	Neuroendocrine hormone levels
	Stool pH <6	Cholestyramine trial
	Avoidance	
	Stool magnesium	

specialized functions of the ileum. Outcomes of ileal resection include diarrhea (from either an excess of bile salts or a deficiency of bile salts, depending on length), vitamin B_{12} deficiency, SIBO (from resection of the ileocecal valve), gallstones (from disruption of the cholesterol pool), and calcium oxalate kidney stones. Normally, in the small bowel, calcium binds to oxalate, and this complex passes into the colon and is excreted in the stool. With a shortened small bowel and absence of the colon, calcium preferentially binds to the fatty acids in the stool, leaving oxalate unbound. Unbound oxalate is incorporated into the stool and excreted through the ostomy. In the case of a shortened small bowel and intact colon, calcium again binds to the fatty acids, and the free or unbound oxalate is absorbed from the colon, leading to the formation of calcium oxalate kidney stones. Although the absolute length of small bowel that is resected is important, the integrity of the remaining bowel is crucial because diffuse pathologic processes such as Crohn disease or radiation enteritis can result in a functionally shortened bowel without surgical resection. Whether a patient has an intact colon is of considerable importance if there has been prior small-bowel resection. The colon can adapt by increasing water and sodium absorption, by acting as an intestinal "brake" to slow motility, and by salvaging nonabsorbed carbohydrates to provide additional calories for patients with short bowel syndrome. Patients who still have an intact colon may not need parenteral nutrition if they have 50 to 100 cm of small bowel remaining. However, patients who no longer have a colon may need parenteral nutrition when the length of the small bowel is less than 150 to 180 cm.

In short bowel syndrome, multiple mechanisms contribute to malabsorption. In the early postoperative stage, hypersecretion of gastric acid inactivates pancreatic enzymes, leading to diarrhea and steatorrhea. Until the remaining small bowel has time to adapt, intestinal transit is rapid because of the loss of surface area. As mentioned above, patients may be at risk for SIBO, and because of the disruption of the enterohepatic circulation of bile, bile acid wasting or steatorrhea (or both) develops. Early management of short bowel syndrome includes aggressive treatment with antidiarrheal agents, total parenteral nutrition, and gastric acid suppression. Later management includes the introduction of a low-fat enteral diet, with progressive increase in carbohydrates, medium-chain triglyceride supplementation as needed, lactose restriction, and treatment of SIBO, if it is present or suspected.

Small-Bowel Diseases

Celiac Disease

Celiac disease may occur in genetically susceptible persons (those with *HLA-DQ2* or *HLA-DQ8* positivity) as an immune response to gliadins in the diet. The prevalence is highest among persons of European descent, and the disease is being diagnosed with greater frequency in North America as clinicians become more familiar with the many manifestations of the disease. In the general population, the prevalence of celiac disease is nearing 1 in 100 (0.7%-1.0%). Among patients with any gastrointestinal symptoms, it is 1 in 56, and among first-degree relatives of a patient with the disease, it is 1 in 22. Celiac disease occurs in patients of all ages, but 20% are older than 60 years at diagnosis.

The diagnosis of celiac disease can be made on the basis of the following: 1) the presence of a clinical feature or features compatible with the disease, 2) supportive serologic studies, 3) characteristic small-bowel biopsy findings, and 4) a clinical response to a gluten-free diet. The diagnosis no longer requires rechallenging the patient with gluten to invoke symptoms because of the risk this presents to highly sensitive patients. Before patients are tested for celiac disease, they need to be eating a gluten-containing diet. While a 6- to 8-week gluten challenge has been recommended in the past, diagnostic changes may be seen as early as 2 weeks after consuming gluten. Testing could be done after 2 weeks on a gluten-containing diet if the patient cannot tolerate a longer interval on the diet; however, if tolerated, 6 additional weeks is recommended before formal testing. Patients with classic celiac disease have features of malabsorption, whereas those with nonclassical celiac disease tend to have extraintestinal manifestations alone. These nonclassical (previously referred to as "atypical") forms of celiac disease now represent the most common clinical presentations of the disease. The gastrointestinal and extraintestinal manifestations of celiac disease are outlined in Table 8.3. The many diseases associated with celiac disease are listed in Table 8.4.

The available serologic tests for evaluating patients for celiac disease measure levels of 1) antigliadin antibodies, 2) endomysial antibodies (EMAs), 3) tissue transglutaminase antibodies (tTGs), and 4) deaminated gliadin peptides (DGPs). The IgA-based tTG test is considered the single best screening test for celiac disease in patients older than 2 years and has a sensitivity of about 95% and a specificity greater than 95%. The native antigliadin antibody test has less sensitivity and specificity than other serologic markers and should be avoided in practice. EMA testing may be more expensive and subjective than tTG testing. IgA deficiency affects 2% to 3% of patients who have celiac disease. In patients with known IgA deficiency, an IgG-based test (IgG tTG or IgG DGP) should be performed. In patients with suspected IgA deficiency, an IgA level can be checked first, with subsequent IgA- or IgG-based serologies checked thereafter according to the IgA level. In children younger than 2 years, EMA and tTG testing may be less sensitive, so a combination of both tTG and DGP testing is recommended in this age group.

Serologic tests for celiac disease should be considered for 1) patients with classic gastrointestinal manifestations of the disease, 2) patients with well-described nonclassic manifestations, 3) at-risk groups, and 4) patients who are being followed for their response to a gluten-free diet. For symptomatic patients, however, biopsy of the small bowel is needed regardless of the results of serologic testing. Also, any positive serologic study needs to be confirmed with small-bowel biopsy studies. Recent guidelines support celiac disease treatment of children without small-bowel biopsies if the children are *HLA-DQ2* positive and have clinical features of celiac disease and a tTG level 10 times the upper limit of normal (confirmed with EMA testing); however, it is still recommended that all adults have histologic diagnostic support of the disease.

The endoscopic findings in celiac disease include loss of mucosal folds, a mosaic pattern, scalloping, and nodularity. The sensitivity of these endoscopic markers is quite poor; however, if the markers are seen, small-bowel biopsy specimens should be obtained regardless of the indication for upper endoscopy because of the high likelihood of demonstrating a pathologic process. Small-bowel biopsy studies are required for the diagnosis of celiac disease and should be performed in all patients before treatment is initiated. The classic histologic findings include villous atrophy (total or partial), crypt hyperplasia, intraepithelial lymphocytosis (>30 intraepithelial lymphocytes per 100 surface enterocytes), and chronic inflammatory cell infiltrate in the lamina propria (Figure 8.1). The spectrum of histologic findings in celiac disease is indicated by the Marsh classification (Figure 8.2). Early Marsh lesions are more likely to produce fewer or no symptoms than late Marsh lesions. An increase in the

Table 8.3. Manifestations of Celiac Disease

Manifestation	*Clinical Features*	*Details*
Gastrointestinal	Diarrhea, steatorrhea	
	Flatulence, distention	
	Weight loss, anorexia	
	Abdominal pain	
	Nausea, vomiting	
	Constipation	
	Aphthous stomatitis	
	Angular cheilosis	
Extraintestinal		
Laboratory findings	Anemia	Deficiencies of iron, vitamin B_{12}, folate (may be normocytic, dimorphic with >1 deficiency)
	Vitamin deficiencies	Examples: vitamins A, D, E, K
	Abnormal liver biochemistry values	Evaluate for AIH, PBC, PSC
Skin	Dermatitis herpetiformis	Pruritic, papulovesicular, on extensor surfaces
Hematologic	Splenic atrophy	Functional, predisposed to encapsulated organisms
Musculoskeletal	Osteopenia, osteoporosis	Calcium or vitamin D loss or lactose avoidance
	Osteomalacia	Vitamin D deficiency, increased bone alkaline phosphatase level
	Enamel defects	Similar to Sjögren syndrome
	Arthropathy	Nonerosive, polyarticular, symmetrical, large joint
	Muscle cramps, tenany	From low calcium, vitamin D, or magnesium levels
Neurologic	Peripheral neuropathy	Symmetrical, distal, small-fiber most common
	Ataxia	Cerebellar
	Epilepsy	Bilateral parieto-occipital calcifications
Reproductive	Infertility	Female or male
	Recurrent miscarriage	
Psychiatric	Depression, anxiety	One-third of celiac patients

Abbreviations: AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.
Data from Farrell RJ, Kelly CP. Diagnosis of celiac sprue. Am J Gastroenterol. 2001 Dec;96(12):3237-46.

Table 8.4. Disorders Associated With Celiac Disease

Type of Disorder	*Disorder*
Endocrine	Type 1 diabetes mellitus
	Autoimmune thyroiditis
Connective tissue disorders	Sjögren syndrome
	Rheumatoid arthritis
	Systemic lupus erythematosus
Immunologic	IgA deficiency
Inflammatory conditions	Inflammatory bowel disease
	Microscopic colitis
Hepatic	AIH, PSC, PBC
Neurologic	Epilepsy
Renal	IgA mesangial nephropathy
Cardiopulmonary	Carditis
	Fibrosing alveolitis
	Pulmonary hemosiderosis
Other	Down syndrome, Turner syndrome

Abbreviations: AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.
Data from Farrell RJ, Kelly CP. Diagnosis of celiac sprue. Am J Gastroenterol. 2001 Dec;96(12):3237-46.

number of intraepithelial lymphocytes is the minimal histologic lesion needed for the diagnosis of celiac disease; villous atrophy alone is not sufficient for diagnosis because it is a nonspecific finding. Other conditions that may show either isolated intraepithelial lymphocytosis or villous flattening in small-bowel biopsy specimens are listed in Box 8.2. These should be considered, especially if the results of serologic studies are negative.

Approximately 95% of patients with celiac disease are positive for *HLA-DQ2*, and the other 5% are positive for *HLA-DQ8*. However, 30% to 40% of the general population is also positive for *HLA-DQ2* or *HLA-DQ8*. Therefore, the presence of one of these permissive genes is necessary but not sufficient for the diagnosis of celiac disease. HLA testing is not necessary for most patients being evaluated for celiac disease; however, the negative predictive value of 100% can be useful in evaluating 1) patients who have early Marsh lesions, 2) patients who have negative serologic results but typical small-bowel histology, 3) patients who already have been prescribed a gluten-free diet and are unwilling to reintroduce gluten in the diet, or 4) at-risk patients (eg, Down syndrome) for whom reporting symptoms may be difficult.

The only treatment for celiac disease is a lifelong gluten-free diet, which includes the avoidance of wheat, barley, and rye. Food items that contain oats can be tolerated by most patients with the disease, but cross-contamination or hypersensitivity may limit oat tolerability. Oats are generally avoided for the first year after diagnosis in symptomatic patients and then reintroduced if the patient is doing well clinically. Consultation with a skilled dietician is imperative for patients with celiac disease. Determining vitamin and mineral levels and providing replacement therapy is recommended. In adults, consideration should be given for bone densitometry. Since patients are at risk for functional asplenia, vaccinations against the encapsulated organisms should be considered.

Dermatitis herpetiformis is an intensely pruritic papulovesicular rash, typically on the extensor surfaces, that represents an intestinal sensitivity to gluten in the diet. Biopsy specimens from the skin adjacent to the affected area may show granular IgA deposits in the papillary dermis; these deposits are pathognomonic for dermatitis herpetiformis (Figure 8.3). Therapy for dermatitis herpetiformis, as for celiac disease, is a lifelong gluten-free diet. Dapsone may help with healing the skin, but it does not heal the intestinal abnormality.

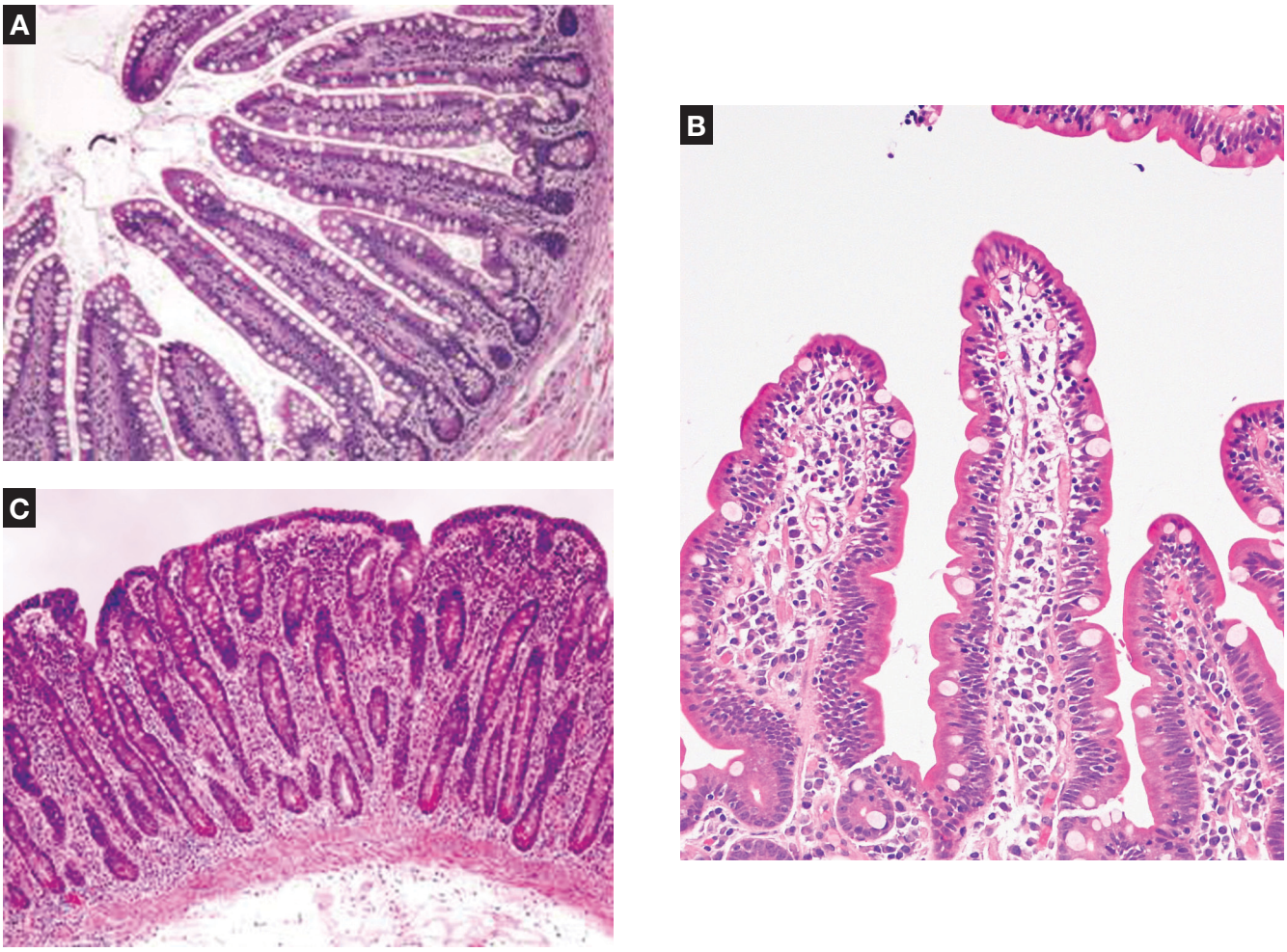

Figure 8.1. Small-Bowel Histopathologic Findings in Celiac Disease. A, Normal findings (hematoxylin-eosin). B, Intraepithelial lymphocytes alone as seen in an early Marsh lesion of celiac disease (hematoxylin-eosin). C, Classic histologic findings of celiac disease, with marked villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis, with a chronic inflammatory cell infiltrate in the lamina propria (hematoxylin-eosin).

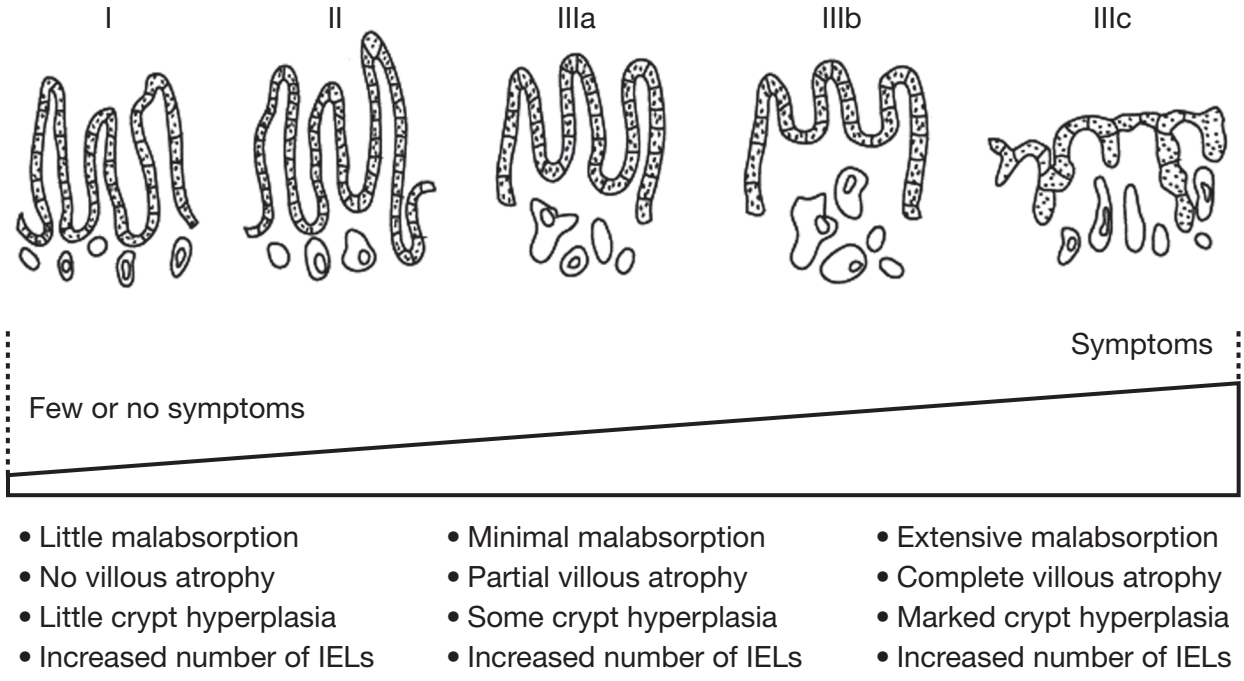

Figure 8.2. Marsh Classification of the Spectrum of Histologic Findings in Celiac Disease. IEL indicates intraepithelial lymphocyte. (Adapted from Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association [AGA] Institute technical review on the diagnosis and management of celiac disease. Gastroenterology. 2006 Dec;131[6]:1981-2002. Used with permission.)

Box 8.2. Causes of Small-Bowel Biopsy Findings That May Mimic Celiac Disease

- Small intestinal bacterial overgrowth
- Nonsteroidal antiinflammatory drugs
- Helicobacter pylori infection
- Giardiasis
- Crohn disease
- Viral gastroenteritis
- Autoimmune enteropathy
- Eosinophilic gastroenteritis
- Combined variable immunodeficiency
- Tropical sprue
- Lymphoma
- Zollinger-Ellison syndrome
- Hypersensitivity to nongluten protein
- Medications (olmesartan)

For patients with celiac disease in whom initial therapy fails or symptoms recur after early clinical improvement, several questions should be answered. First, was the initial diagnosis of celiac disease correct? Results of the small-bowel biopsies and supportive serologic studies should be reviewed. Second, has there been inadvertent or surreptitious ingestion of gluten? The ingestion of gluten is the most likely cause of ongoing or recurring symptoms in a patient with celiac disease; thus, the patient's diet and medications should be reviewed. Also, patients with celiac disease are at risk for other conditions that can cause diarrhea, and these should be considered: microscopic colitis, SIBO, pancreatic insufficiency, lactase deficiency, and inflammatory bowel disease. Celiac-specific complications also need to be considered, including ulcerative jejunitis, refractory sprue, and malignancy. Patients with celiac disease are at increased risk for enteropathy-associated T-cell lymphoma (EATL), which may be manifested as a recurrence of symptoms. EATL is associated with poor survival. Compliance with a gluten-free diet can significantly reduce the risk of EATL. Other malignancies for which patients with celiac disease are at increased risk include other forms of non-Hodgkin lymphoma, small-bowel adenocarcinoma, and oropharyngeal and esophageal cancers.

Whipple Disease

Whipple disease is a multisystem disorder caused by the gram-positive bacillus *Tropheryma whipplei*. This disease usually occurs in white men in the fourth or fifth decade of life. The clinical features include diarrhea, weight loss, adenopathy, arthralgias, fevers, carditis, hyperpigmentation, pleural effusions, and ocular and neurologic symptoms. The diagnosis can be established with a combination of small-bowel biopsy studies and the polymerase chain reaction (PCR). Small-bowel biopsy specimens typically contain periodic acid-Schiff (PAS)-positive macrophages (Figure 8.4). *Tropheryma whipplei* needs to be differentiated from *Mycobacterium avium-intracellulare* complex, which, in addition to being PAS-positive, is also acid-fast–positive. Electron microscopy can be used to show sickle-shaped

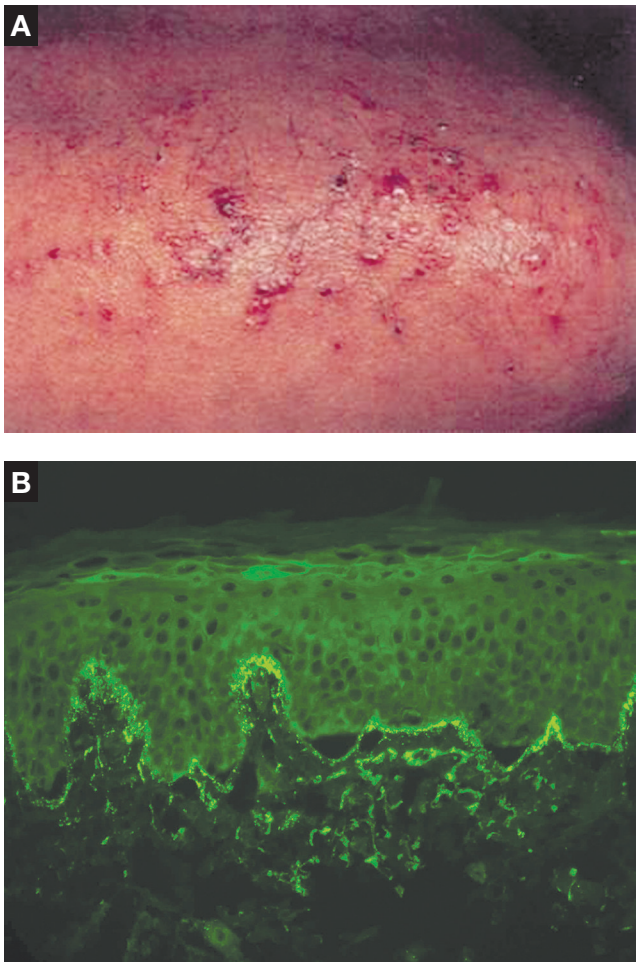

Figure 8.3. Dermatitis Herpetiformis. A, Pruritic papulovesicular rash on the extensor surface of the skin. (Adapted from Bennett ML, Jorizzo JL, Sherertz EF. Skin lesions associated with gastrointestinal and liver diseases. In: Yamada T, editor. Textbook of gastroenterology. 4th ed. Vol 1. Philadelphia [PA]: Lippincott Williams & Wilkins; c2003. p. 992-1009. Used with permission.) B, Immunofluorescence of biopsy specimen showing the characteristic IgA deposits in the papillary dermis. (Courtesy of Dr Kristin M. Leiferman, Immunodermatology Laboratory, University of Utah. Used with permission.)

T whipplei bacteria with their trilaminar cell wall. If the biopsy specimens are PAS-positive and PCR is positive, the diagnosis is established. A testing algorithm is provided in Figure 8.5. Treatment of Whipple disease includes long-term treatment with antibiotics that penetrate the blood-brain barrier. In a randomized controlled study, 14 days of intravenous therapy with either ceftriaxone or meropenem, followed by 1 year of oral trimethoprim-sulfamethoxazole, was curative. Therapies that have had variable success include doxycycline, hydroxychloroquine, and interferon-based regimens.

Tropical Sprue

Tropical sprue may have features that are indistinguishable from those of classic celiac disease, with diarrhea, weight loss, anorexia, and lactose intolerance. Tropical sprue needs to be considered if the patient has traveled to certain geographic areas, such as Asia, India, the Caribbean, and Central or South America. In patients with acute tropical sprue, the onset of clinical features

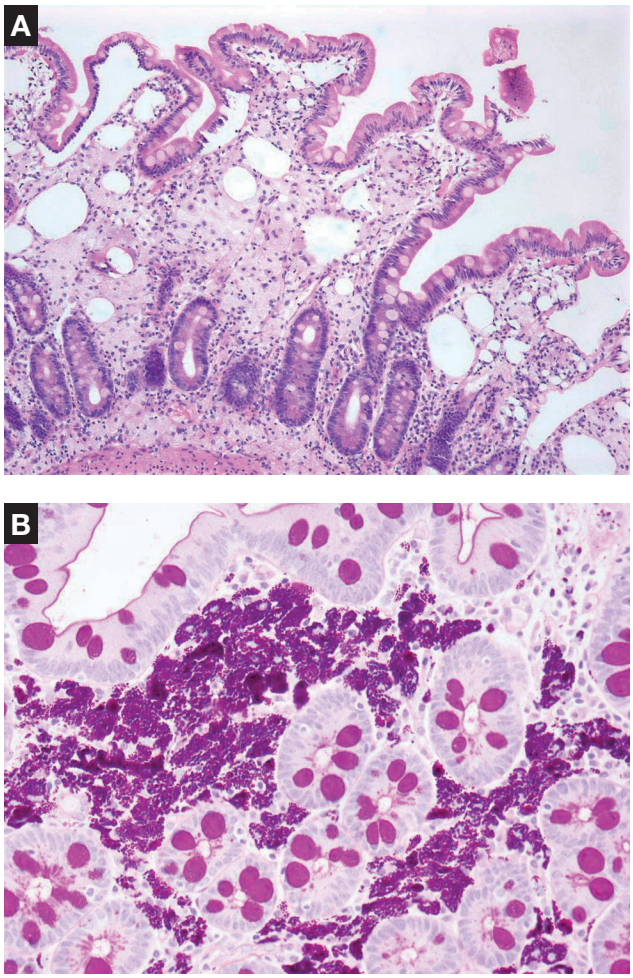

Figure 8.4. Histopathologic Features of Whipple Disease. A, Note the widened villi (hematoxylin-eosin). B, The villi are filled with foamy macrophages that are periodic acid-Schiff–positive.

is rapid and is independent of the length of stay in a tropical area. By comparison, in patients with chronic tropical sprue, clinical features occur gradually after several years of residence in a tropical area. Physical examination may show evidence of weight loss or cachexia, glossitis, and hyperactive bowel sounds. Laboratory features can indicate megaloblastic anemia with vitamin B_{12} and folate deficiency and a protein-losing state. No specific test helps establish the diagnosis, and other infectious disorders need to be ruled out. Small-bowel biopsy specimens may show villous atrophy similar to that apparent in celiac disease; therefore, for all patients with newly diagnosed celiac disease, the travel history needs to be documented, especially if the serologic test results are negative. Treatment with folate, 5 mg daily, and vitamin B_{12} replacement produces rapid improvement in the anemia, glossitis, and weight loss in many patients with tropical sprue. In addition, antibiotic therapy with tetracycline, 250 mg 4 times daily, may be needed in combination with folate for 3 to 6 months, especially to treat the chronic form of the disease.

Eosinophilic Gastroenteritis

Eosinophilic gastroenteritis has various clinical manifestations depending on the location of bowel involvement. With mucosal disease, patients often have diarrhea, malabsorption, and evidence of a protein-losing enteropathy. Involvement of the muscularis layer may lead to features of bowel obstruction, whereas serosal involvement may lead to ascites and peritonitis.

Laboratory studies typically show an increased serum level of IgE and peripheral eosinophilia, with a more marked increase in the serum eosinophil count in patients with serosal disease. However, a normal serum eosinophil count does not exclude eosinophilic gastroenteritis. With the mucosal form of the disease, the diagnosis is established with intestinal biopsy specimens that show more than 20 to 25 eosinophils per high-power field. With muscular or serosal involvement, a full-thickness biopsy may be required. Eosinophilia found on ascitic fluid analysis also can be suggestive. Parasitic infections need to be ruled out before eosinophilic gastroenteritis is diagnosed. Also, eosinophilic gastroenteritis needs to be differentiated from hypereosinophilic syndrome, which is characterized by a serum eosinophil count greater than 1.5×10^9/L for more than 6 months and multiorgan involvement.

An elimination diet may be incorporated in the treatment program for eosinophilic gastroenteritis, although it has a limited role. Prednisone, 20 to 40 mg orally daily, often produces a prompt clinical response, regardless of the layer of bowel involved. Treatment with mast cell stabilizers, such as sodium cromoglycate, and leukotriene receptor antagonists, such as montelukast, has had variable success. Although budesonide can be given in place of low-dose prednisone to patients who require ongoing maintenance therapy, the controlled-release formulation of this medication may not provide adequate therapy to the proximal gastrointestinal tract. The monoclonal antibody omalizumab has provided symptomatic benefit to some patients.

Intestinal Lymphangiectasia

Intestinal lymphangiectasia occurs as either a primary form or a secondary form. Primary lymphangiectasia is characterized by diffuse or localized ectasia of the enteric lymphatic system and often is diagnosed at a young age. Secondary lymphangiectasia occurs with conditions that produce impaired lymphatic flow; the causes are cardiac (congestive heart failure or constriction), neoplastic (lymphoma), or structural (retroperitoneal fibrosis). Patients present with pronounced edema, diarrhea, nausea, and vomiting; also, chylothorax and chylous ascites may be present. Steatorrhea may be concurrent with a protein-losing enteropathy. Laboratory findings include a decrease in the plasma level of proteins and lymphocytopenia, which may affect cellular immunity. Endoscopically, punctate white dots may be seen on the bowel mucosa; histologic examination shows marked dilatation of the lacteals (Figure 8.6). Abnormalities of the lymphatics may also be assessed with contrast lymphangiography or nuclear scintigraphy after a high-fat load. The protein-losing state can be verified with an α_1-antitrypsin clearance test (described above).

Treatment of the primary form includes a low-fat, high-protein diet and supplementation with medium-chain triglycerides as needed. If the disease is localized, resection could be considered. For the secondary form, treatment should be directed at the underlying disease process.

Amyloidosis

Amyloidosis is a multisystem disease that frequently involves the gastrointestinal tract. Amyloid deposits can be found at various levels of the bowel wall, although they usually are detected in the submucosa. Amyloid also can be deposited in neuromuscular or

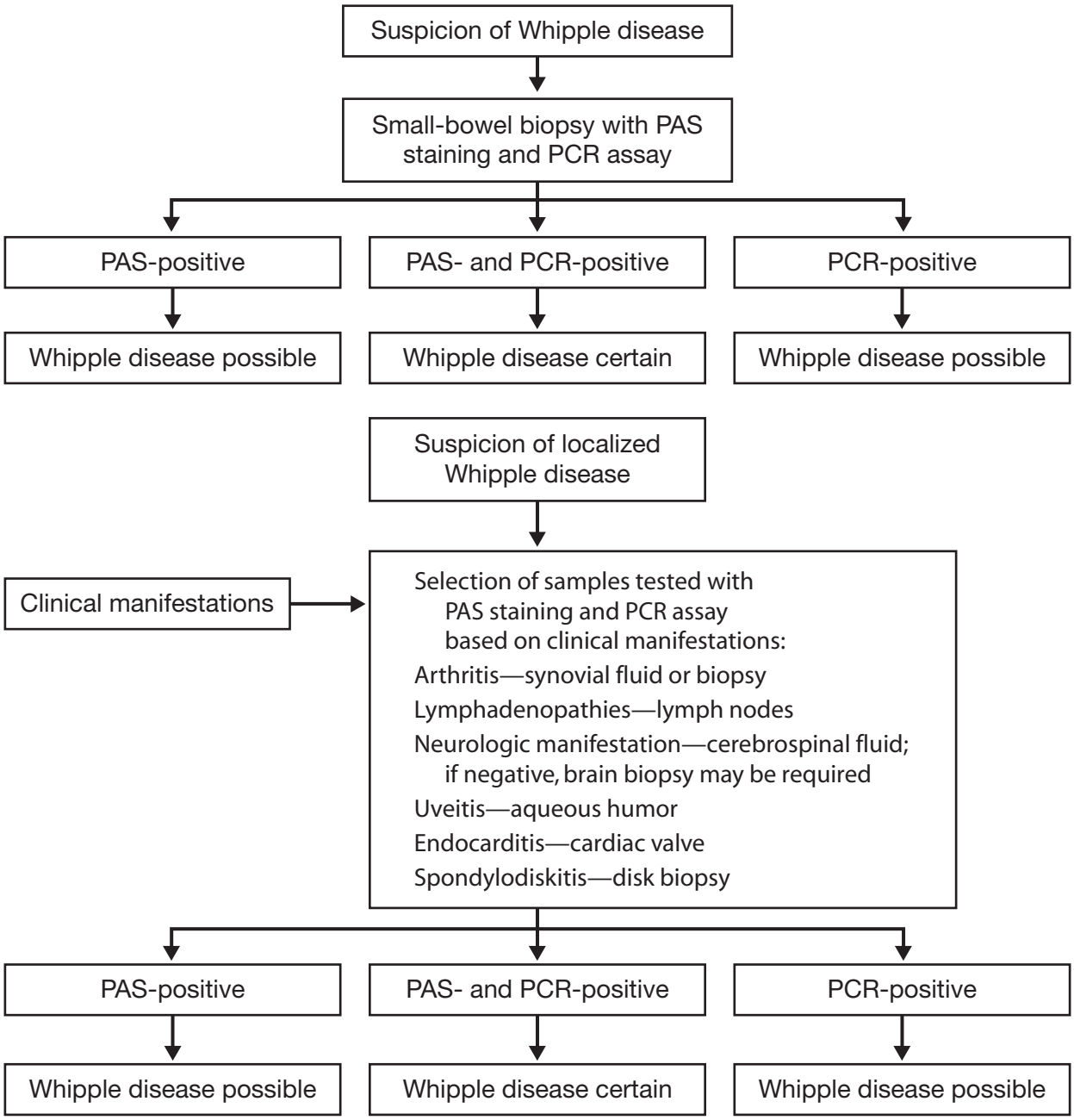

Figure 8.5. Strategy for Diagnosing Whipple Disease by Using Periodic Acid-Schiff (PAS) Staining and the Polymerase Chain Reaction (PCR) Assay. (Adapted from Fenollar F, Puechal X, Raoult D. Whipple's disease. N Engl J Med. 2007 Jan 4;356[1]:55-66. Used with permission.)

perivascular sites. Patients with amyloidosis may have diarrhea for many reasons. There may be delayed or accelerated transit related to autonomic neuropathy, which may lead to SIBO or bile acid malabsorption, respectively. Also, the amyloid deposits may act as a barrier that prevents proper absorption; patients can have a combination of fat, protein, or carbohydrate malabsorption. They commonly have lactose malabsorption. The endoscopic findings in amyloidosis include granularity, friability, and erosions, but they are often normal. The yield of detecting amyloidosis involvement of the gastrointestinal tract depends on the site from which biopsy samples are obtained: esophagus 70%, stomach 75% to 95%, small intestine 85% to 100%, and colorectum 75% to 95%. A fat aspirate can be obtained for diagnostic purposes, but this may have a lower yield than intestinal biopsies if there is clinical suggestion of involvement of the gastrointestinal tract. Congo red staining can show apple-green birefringence, which is seen best in the walls of the vasculature if the biopsy specimens contain lamina propria. Treatment of amyloidosis involvement of the gastrointestinal tract includes treating the underlying disease, but treatment of SIBO and lactose avoidance should be considered.

Other Conditions

Scleroderma

Patients with systemic scleroderma may have diarrhea and malabsorption from gastrointestinal disease. The diarrhea may be due to ineffectual motility, which may lead to SIBO. Also, chronic intestinal pseudo-obstruction may occur with systemic scleroderma.

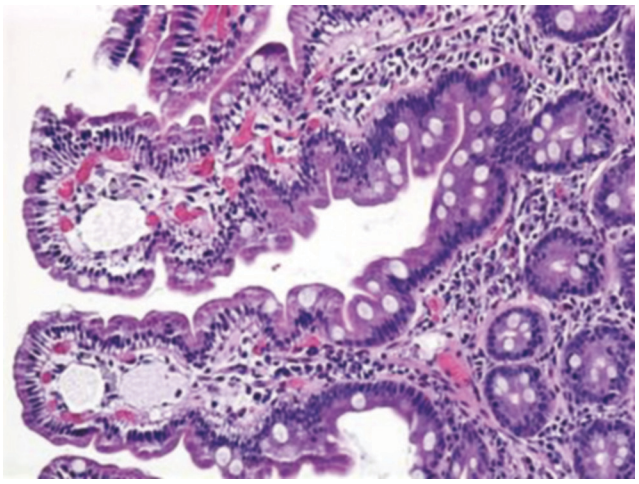

Figure 8.6. Lymphangiectasia. Note the dilated lacteals in several contiguous villi (hematoxylin-eosin).

In addition, diarrhea may occur from decreased mucosal blood flow due to vasospasm, or diarrhea may result from lactose malabsorption. Treatment of diarrhea in patients with scleroderma includes antibiotics for SIBO and a lactose-restricted diet, as indicated. Treatment with low-dose octreotide, 50 µg at bedtime, could be considered because it can help stimulate intestinal motility and improve symptoms; however, octreotide can be prohibitively expensive.

Diabetes Mellitus

Patients with diabetes mellitus may present with diarrhea or malabsorption (or both) for various reasons. First, several oral hypoglycemic agents, such as metformin and acarbose, are associated with diarrhea; the relation between the initiation of treatment with these medications and the onset of diarrhea needs to be determined. Second, delayed intestinal transit in patients with diabetes puts them at risk for SIBO. Third, because of the increased prevalence of celiac disease among patients with type 1 diabetes mellitus, celiac disease needs to be considered. Fourth, pancreatic insufficiency needs to be considered because it may explain not only the diarrhea but also the hyperglycemia. Fifth, patients with diabetes may ingest a significant amount of sugar-free substances for better glycemic control; these substances often contain sorbitol, xylitol, or other sugar alcohols that may induce osmotic diarrhea. Sixth, in patients who have diabetes with end-organ involvement, an autonomic neuropathy may develop that will affect the gastrointestinal tract and lead to "diabetic diarrhea," for which clonidine therapy may be helpful if the patient does not have orthostatism.

Hospitalized Patients

New diarrhea or malabsorption in hospitalized patients has a broad differential diagnosis that includes the following: antibiotics, *Clostridium difficile* infection, tube feedings (based on the location of the tube in the bowel, concentration of the formula, and bolus effect of the nutrition), elixir medications (which contain sorbitol), magnesium (as in antacids and magnesium replacement or supplementation), intestinal ischemia (especially in critically ill patients), and fecal impaction with secondary overflow. Also, use of any new medication that was started during the hospitalization should be scrutinized as a cause of new-onset diarrhea. Diarrhea that is long-standing or was present before hospitalization requires diagnostic evaluation for chronic diarrhea (which can be done in the outpatient setting).

Miscellaneous

Many other conditions are associated with diarrhea, malabsorption, and mucosal disease of the small bowel but cannot be considered in detail here. Conditions to review include immunodeficiencies (IgA deficiency, combined variable immunodeficiency, and graft-versus-host disease), autoimmune enteropathy, collagen vascular diseases and vasculitides, radiation enteritis, ischemia, mastocytosis, abetalipoproteinemia, and endocrinopathies (thyroid and adrenal).

Bacterial Overgrowth Syndromes

Normally, the small-bowel flora contains a relatively small number of bacteria ($<10^3$ organisms/mL), with a predominance of gram-positive organisms. In contrast, the colonic flora has a significantly higher concentration of bacteria, which are largely gram-negative and anaerobic organisms. When there is stasis, altered motility, or loss of protective defenses in the proximal intestinal tract, bacteria that are more representative of colonic flora can overgrow in the small bowel and result in SIBO, a syndrome of diarrhea and nutritional deficiencies.

The many risk factors for SIBO are listed in Table 8.5, with the principal causes associated with stasis of small-bowel contents or loss of protective gastric acid. Structural or surgical changes in the bowel that produce relative stasis or reflux of colonic flora into the small bowel can be obtained from the history and radiographic imaging of the small bowel. Any motility disorder that affects the small bowel (scleroderma, diabetes mellitus, or pseudo-obstruction) can lead to stasis and overgrowth. Gastric

Table 8.5. Risk Factors for Small Intestinal Bacterial Overgrowth

Category	*Risk Factor*
Structural	Small-bowel diverticula
	Intestinal strictures (Crohn disease, radiation, NSAIDs)
	Enterocolonic fistula
Surgical	Blind loops, afferent limbs
	Ileocecal valve resection
Dysmotility	Chronic intestinal pseudo-obstruction
	Scleroderma
	Gastroparesis
	Diabetic autonomic neuropathy
Diminished acid	Achlorhydria, gastric atrophy
	Gastric resection
	Acid suppression (PPI therapy)
Others	Cirrhosis
	Pancreatitis
	Immunodeficiencies
	Celiac disease
	Advanced age
	Idiopathic

Abbreviations: NSAID, nonsteroidal antiinflammatory drug; PPI, proton pump inhibitor.
Adapted from Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. Gastroenterol Hepatol (NY). 2007 Feb;3(2):112-22. Used with permission.

acid is thought to be a protective barrier that keeps pathogenic bacteria out of the small intestine; when there is loss of gastric acid, SIBO may ensue. Advanced age alone may be a factor. In many patients, no discrete risk factor is identified.

Symptoms of SIBO include abdominal pain, bloating, flatulence, diarrhea, and weight loss. Malabsorption of fat, protein, or carbohydrates (or a combination of these) can occur with secondary diarrhea. Fat malabsorption results from bacterial deconjugation of bile salts and leads to steatorrhea. Carbohydrate malabsorption can occur because of early sugar breakdown and fermentation from bacteria as well as from decreased disaccharidase activity caused by mucosal damage and bacterial by-products. Mucosal damage is thought to have a role in protein malabsorption because of the effect on oligopeptidase levels.

A classic pattern of laboratory findings in SIBO includes a low serum level of vitamin B_{12} and an increased serum level of folate. The low level of vitamin B_{12} is the result of bacteria cleaving vitamin B_{12} prematurely from intrinsic factor and from the competitive binding and consuming of vitamin B_{12} by anaerobic bacteria. In this instance, results of the Schilling test should normalize after the administration of antibiotics. The increased serum level of folate is the result of folate synthesis by the intestinal bacteria. In addition to the above laboratory findings, serum levels of iron, protein, albumin, and fat-soluble vitamins may be low, depending on the degree of malabsorption.

The reference standard for making the diagnosis of SIBO is small-bowel cultures from direct aspiration of the jejunum, with more than 10^5 organisms/mL of aerobes and anaerobes being diagnostic. Limitations of small-bowel cultures include availability, lack of excess intestinal secretions for aspiration, recent antibiotic therapy, and decreased or no reimbursement for the test. Also, breath testing can be used to diagnose SIBO, with lactulose hydrogen, glucose hydrogen, or ^{14}C-xylose substrates, in which an oral load of the substrate is given and breath hydrogen concentration is measured every 15 to 30 minutes for 2 to 4 hours. Either glucose or lactulose hydrogen breath testing can be safely performed in children or pregnant women. A diagnosis of SIBO is supported by an increase of more than 12 or 20 parts per million above baseline for glucose and lactulose, respectively, during the first 90 minutes. An increase is seen again as these substances reach the colon, thus producing a "double peak" that also can be used as a criterion for diagnosis (Figure 8.7). False-positive results of breath testing can result from rapid intestinal transit, in which the carbohydrate substance rapidly reaches the colon and produces an early but not double-peaked pattern. False-negative results of breath testing can occur from recent antibiotic therapy. Also, the results are falsely negative in 20% of the population who have methogenic colonic bacteria; in these cases, breath methane levels rather than hydrogen levels can be checked. Breath testing results also can be affected by recent laxative use, high carbohydrate consumption, recent intense physical activity, and smoking. Once SIBO is diagnosed on the basis of cultures or breath testing, evaluating for predisposing conditions could be considered. Also, an empirical trial of antibiotics could be considered for patients in whom testing for SIBO may not be available or may lead to inaccurate results.

Treatment of SIBO lies in managing the symptoms and replacing the deficiencies. Although modifying the underlying risk factor that predisposes to SIBO is feasible in only a small fraction of patients, it should be considered (tighter glycemic control in diabetic patients, surgery for patients with stricturing disease, and possibly octreotide for patients with scleroderma). Vitamin and mineral levels should be measured and deficiencies corrected before irreversible sequelae ensue (eg, as with vitamin B_{12} deficiency). The role of antibiotic therapy is not to sterilize the small bowel but rather to decrease and modify the bacterial makeup so that it more closely resembles the flora that should be present in the small intestine, with therapy targeting gram-negative and anaerobic organisms. Various antibiotics have been used, such as amoxicillin-clavulanate, fluoroquinolones, rifaximin,

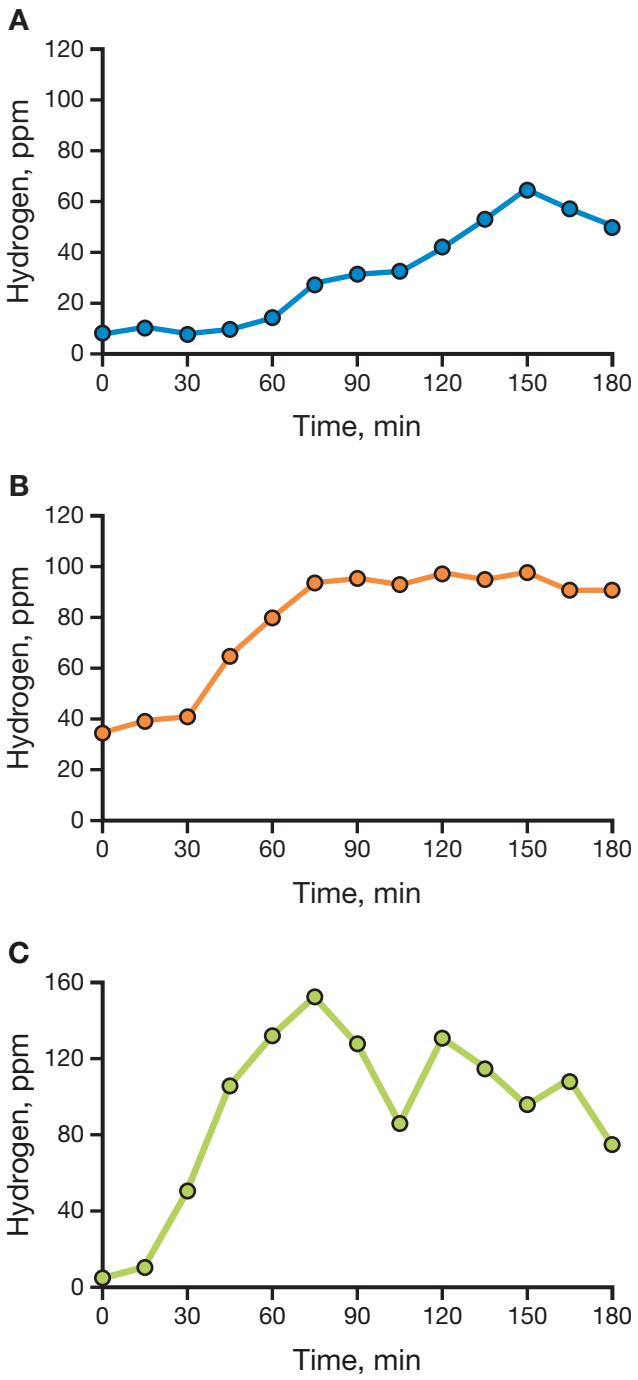

Figure 8.7. Breath Testing Patterns for Small Intestinal Bacterial Overgrowth. A, Lactulose breath test without bacterial overgrowth. B, Lactulose breath test with bacterial overgrowth. C, Lactulose breath test showing double-peak pattern. (Adapted from Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. Gastroenterol Hepatol [NY]. 2007 Feb;3[2]:112-22. Used with permission.)

tetracycline derivatives, and metronidazole. Initial treatment may consist of 7 to 10 days of an antibiotic, with repeated courses when symptoms recur. Some patients may need monthly rotating antibiotic therapy, while others may not require retreatment for many months. Also, modified lactose intake should be considered in those with ongoing symptoms after antibiotic therapy, given the damaging effects that can be seen on the small-bowel microvilli due to SIBO.

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9

Nutritional Disorders: Vitamins and Minerals

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Vitamins and minerals are critical to normal health because they are essential to a vast assortment of metabolic functions. This chapter focuses on selected important vitamins and minerals and their relationships with gastrointestinal tract disorders.

Water-Soluble Vitamins

Vitamin B_{12}

Dietary intake of vitamin B_{12} (cobalamin) requires the ingestion of animal products (meat, dairy, fish, and shellfish). Although adults require only 2.4 mcg daily, most adults in developed countries ingest 5 to 15 mcg daily. Only slightly more vitamin B_{12} is required during pregnancy (2.6 mcg daily) and lactation (2.8 mcg daily).

Because cobalamin is bound to animal proteins, it must be released. Gastric contractions, gastric acid, and gastric pepsins accomplish this function. Free vitamin B_{12} then binds to salivary and gastric R proteins (haptocorrins), a process that is facilitated by the acid pH in the stomach. The production and secretion of intrinsic factor by gastric parietal cells are critical for the transfer of cobalamin from haptocorrins to intrinsic factor, which occurs in the duodenum and is facilitated by pancreatic proteases (degradation of haptocorrins) and the more neutral pH of the duodenum. Finally, in the terminal ileum, the cobalamin–intrinsic factor complex is bound to specific receptors and vitamin B_{12} is absorbed into the circulation, where it binds to transcobalamin II. About one-half of the circulating vitamin B_{12} in cobalamin–transcobalamin II is secreted into bile, of which one-half is recycled and the other half is excreted in stool. Cobalamin in bile is bound to a biliary haptocorrin, and this binding protein is then degraded by pancreatic proteases in the duodenum, once again liberating vitamin B_{12} for its binding to intrinsic factor. In healthy persons, overall about 70% of ingested cobalamin is absorbed.

Deficiency of vitamin B_{12} results in megaloblastic anemia and hyperhomocystinemia, identical to that in folic acid deficiency. In contrast to folic acid deficiency, vitamin B_{12} deficiency can cause neuropsychiatric abnormalities, including dementia, and disorders such as ataxia, paresthesia, chorea, dystonia, subacute combined degeneration of the posterior columns of the spinal cord (loss of lower extremity vibratory and sometimes proprioceptive sensation), and loss of taste sensation. Both vitamin B_{12} deficiency and folate deficiency can cause glossitis, anorexia, and diarrhea.

Serum methylmalonic acid levels (normal in folic acid deficiency) may be increased (abnormal) before vitamin B_{12} levels are subnormal. Because large amounts of cobalamin (2.0-2.5 mg) are stored in the body, especially in the liver, the lack of adequate dietary vitamin B_{12} (eg, in a person who decides to be a true vegan, without supplements) may take years to cause cobalamin deficiency.

Achlorhydria is a common cause of vitamin B_{12} deficiency in the elderly. Pernicious anemia is another not uncommon cause of vitamin B_{12} deficiency because of the lack of intrinsic factor and acid. In contrast to achlorhydria, hyperacidity (as in Zollinger-Ellison syndrome) can disrupt the duodenal phase of cobalamin absorption (by lack of a more neutral pH and inactivation of pancreatic proteases) and result in cobalamin deficiency. Vitamin B_{12} deficiency rarely occurs with pancreatic insufficiency itself or with long-term treatment with acid-suppressive medications. Bacterial overgrowth, infestation with *Diphyllobothrium latum*, and ileal disease (Crohn disease and radiation enteritis) or resection also can result in vitamin B_{12} deficiency. Often, gastric bypass surgery is complicated by subsequent cobalamin

deficiency (lack of intrinsic factor, acid, and gastric grinding function). Chronic use of the antidiabetic agents metformin and phenformin can decrease absorption of cobalamin, resulting in vitamin B_{12} deficiency.

Pitfalls of the Schilling test include the use of crystalline (not food-bound) cobalamin, which bypasses the first step in vitamin B_{12} absorption (release of cobalamin from its food-bound state, as in elderly persons with achlorhydria), false-normal values, and abnormal ileal absorption due to ileal macrocytosis (ongoing uncorrected cobalamin deficiency).

Cobalamin deficiency, especially that due to pernicious anemia, gastrectomy, or ileal disease, generally is treated with parenteral cobalamin—1 mg daily for a week, then once weekly for a few weeks, and then once monthly. High-dose oral cobalamin (1-2 mg daily) has a role in patients after cobalamin stores have been repleted, or as initial therapy in persons who have a residual ability to absorb cobalamin and a mild cobalamin deficiency.

Folic Acid

Folic acid (vitamin B_9) has many dietary sources, including green leafy vegetables, grains, orange juice, and organ meats. Adults should ingest 400 mcg daily of folic acid. In pregnancy, 600 mcg daily is recommended, and 500 mcg daily is required during lactation. Brush border membrane hydrolysis of dietary folylpolyglutamates is followed by active transport of folylmonoglutamates, principally in the duodenum and upper jejunum.

Folic acid deficiency may lead to megaloblastic anemia, diarrhea (macrocytic enterocytes), glossitis, neural tube defects in newborns (maternal folic acid deficiency in the first 2 weeks of pregnancy), and increased risk of colorectal cancer and cardiovascular disease. Persons at increased risk of folic acid deficiency are those with a dietary deficiency of folic acid (body stores may last for up to 4 months), intestinal malabsorption states (small-bowel diseases, drugs such as sulfasalazine, phenytoin, methotrexate, and alcohol), pregnancy, lactation, chronic hemolytic anemia, malignancy, or chronic liver disease. Long-term use of medications such as methotrexate, phenytoin, and trimethoprim can cause folic acid deficiency.

Folic acid by mouth, 1 to 5 mg daily, should be given for several weeks to persons with folic acid deficiency. Cobalamin deficiency needs to be ruled out or treated before folic acid therapy is begun.

Other Water-Soluble Vitamins

Vitamin C deficiency results in scurvy (men require 90 mg daily, women 75 mg daily, pregnant women 80 mg daily, lactating women 120 mg daily). Clinical features may include perifollicular hyperkeratotic papules and petechiae; swollen, red, bleeding gums; or anemia. Persons who smoke require more vitamin C (men 120 mg daily, women 110 mg daily). Severe malabsorptive disease and chronic alcoholism increase the risk of vitamin C deficiency. Vitamin C supplementation enhances iron absorption and can increase the risk of adverse cardiovascular events in persons with advanced iron storage disease (hemochromatosis). Supplementation with more than 250 mg daily of vitamin C also can produce false-negative results on fecal occult blood tests and increase the risk of hyperoxaluria and kidney stones in persons with chronic renal disease.

Thiamine (vitamin B_1) deficiency can result in wet beriberi with cardiac abnormalities (cardiomyopathy and high-output failure) or dry beriberi with neurologic disorders (peripheral neuropathy, cerebellar dysfunction, gaze pareses, or Wernicke-Korsakoff syndrome), which may be exacerbated by the administration of glucose to thiamine-deficient patients. Chronic alcoholism, overuse of diuretics, long-term renal dialysis, pregnancy, malabsorptive disorders (including gastric bypass surgery), and chronic malnutrition all are risk factors for thiamine deficiency. A little more than 1.0 mg daily is required. Thiamine is found in grains and pork.

Riboflavin (vitamin B_2) deficiency can cause angular stomatitis, cheilosis, glossitis, seborrheic dermatitis, peripheral neuropathy, and impaired vision. Chronic alcoholism and malabsorptive disorders are risk factors. Fortified cereals, milk, and eggs provide riboflavin. Slightly more than 1.0 mg daily is required.

Niacin (vitamin B_3) deficiency due to malabsorptive syndromes, chronic alcoholism, carcinoid syndrome, or drug therapy (isoniazid, 6-mercaptopurine, or azathioprine) can produce pellagra (diarrhea, dermatitis, and dementia), glossitis, cheilosis, dyssebacia, and angular stomatitis. Tryptophan, fortified cereals, legumes, and fish are sources of niacin; between 14 and 18 mg of niacin equivalent is needed daily. Excess niacin (such as crystalline nicotinic acid) can cause flushing and diarrhea and can worsen peptic ulcer disease. It also can lead to hepatocellular injury.

Pyridoxine (vitamin B_6) deficiency can occur in patients receiving treatment with isoniazid, cycloserine, hydralazine, oral contraceptives, dopamine, or D-penicillamine. Malabsorptive syndromes and chronic alcoholism also are risk factors. Glossitis, cheilosis, angular stomatitis, seborrheic dermatitis, sideroblastic anemia, seizures, and peripheral neuropathy may supervene. Vitamin B_6 deficiency may be responsible for both the limited increase in aminotransferase values and the increased ratio of aspartate aminotransferase to alanine aminotransferase in alcoholic hepatitis. Pyridoxine occurs in meat, fish, fortified cereals, and noncitrus fruit. Between 1.3 and 2.0 mg is required daily. Massive doses may cause sensory neuropathy.

Although biotin deficiency is rare, it can occur in patients receiving total parenteral nutrition without biotin supplementation. Altered mental status, metabolic acidosis, and seborrheic dermatitis may occur.

Fat-Soluble Vitamins

Vitamin A

As with other fat-soluble vitamins, the absorption of vitamin A requires luminal bile salts and pancreatic esterases, assembly into chylomicrons, and lymphatic transport. Daily requirements in adults range from about 2,500 to 5,000 international units. Lack of vitamin A can produce night blindness, xerophthalmia, a follicular hyperkeratotic rash, abnormalities of taste and smell, bone and muscle pain, and increased risk of infections. Liver disease may be accompanied by vitamin A deficiency, especially alcoholic liver disease. However, persons with alcoholic liver disease and vitamin A deficiency who receive vitamin A supplementation are at risk for hepatotoxicity. Similar to other fat-soluble vitamins, excess vitamin A can cause toxicity (liver failure, increased cerebrospinal fluid pressure, desquamating rash, alopecia, or hypercalcemia).

Vitamin D

Adequate vitamin D levels are achieved with diet, dietary supplementation, and sunlight. Liver disease and kidney disease, as well as malabsorptive conditions, are the major risk factors for vitamin D deficiency. Excess vitamin D can result in anorexia,

nausea, vomiting, constipation, confusion, and abdominal pain (hypercalcemia) and polyuria and kidney stones (hypercalciuria).

Vitamin E

Malabsorptive disorders and particularly chronic cholestasis in children are major risk factors for vitamin E deficiency. Manifestations of vitamin E deficiency include neurologic symptoms (posterior column disease, peripheral neuropathy, and brainstem and cranial nerve damage), retinal disease, and hemolysis. High doses of vitamin E may cause coagulation disorders.

Vitamin K

Vitamin K is acquired from exogenous dietary sources (green leafy vegetables) and endogenous sources (intestinal bacteria). Malabsorptive syndromes, dietary inadequacy, and antibiotic administration are risk factors for vitamin K deficiency. Factor VII usually is the rate-limiting factor for normal prothrombin time (or the international normalized ratio). Excessive doses of vitamin E can interfere with vitamin K–dependent metabolism, resulting in hemorrhage.

Minerals

Iron

Loss of endogenous iron from the gastrointestinal tract (usually 1.0-2.0 mg daily), urinary tract, and skin and menstrual loss in women needs to be matched by iron absorption from the duodenum and upper jejunum. Men and postmenopausal women require 8 mg daily, and premenopausal women require 15 to 18 mg daily. Iron contained in the form of heme from meat is absorbed more readily (up to 25%) than inorganic ferric iron salts (3%-10%). Gastric grinding, gastric acid, and gastric ascorbate help make ferric iron compounds more soluble. Ferric reductase (duodenal cytochrome B) on the brush border and ascorbate reduce inorganic iron from the ferric form (Fe^{3+}) to the ferrous form (Fe^{2+}). An iron transporter, divalent metal transporter 1, also on the brush border, facilitates the absorption of ferrous iron. This same transporter also can facilitate the absorption of divalent copper, zinc, lead, and manganese, each of which can compete with and inhibit the absorption of divalent iron. Ferroportin 1 along with ferroxidase hephaestin (both located on the basolateral membrane) transports iron into the circulation, oxidizes it to the ferric form, and allows it to bind to apotransferrin, forming transferrin. The liver produces hepcidin, which regulates iron transport through its interactions with ferroportin 1, decreasing iron absorption. The basolateral membrane transferrin receptor, under regulation by the hemochromatosis gene *HFE*, allows intestinal cell reuptake of iron from transferrin. Normally, with adequate total body iron stores, up to about 10% of dietary inorganic iron can be absorbed. With iron deficiency, this may increase to 30%.

Iron deficiency can result in microcytic hypochromic anemia, altered immune function, angular stomatitis, koilonychia, and atrophic lingual papillae. Contributors to iron deficiency include lack of dietary iron, increased gastrointestinal loss of iron (bleeding), poor absorption of iron (upper small-bowel mucosal dysfunction as in celiac disease), bypass of the upper small bowel (gastrojejunal bypass surgery), gastric resection and achlorhydria, and persistent ingestion of iron-binding compounds (soil or laundry starch). (Iron overload is discussed in Chapter 29, "Metabolic Liver Disease.")

Zinc

Zinc is required as a cofactor for many enzymes (eg, alkaline phosphatase), and its deficiency impairs growth, development, and reproductive and immune functions. Between 8 and 14 mg is required daily. Meat and seafood are good sources. Risk factors for zinc deficiency are chronic diarrhea, short bowel syndrome, cystic fibrosis, pancreatic insufficiency, cirrhosis, alcoholism, chronic renal failure, anorexia nervosa, pregnancy, sickle cell anemia, and use of the drug D-penicillamine. A scaly red rash involving the face, groin, and hands may occur with zinc deficiency itself or as a result of the autosomal recessive disorder of zinc metabolism, acrodermatitis enteropathica. Alopecia, loss of taste sensation, growth retardation, poor wound healing, hypogonadism, diarrhea, and night blindness also may occur from zinc deficiency. Excess zinc intake (eg, supplements such as those used to treat Wilson disease) can cause copper deficiency.

Copper

Copper occurs in meat, nuts, and grains. Nearly 1 mg is required daily. Copper deficiency can result in microcytic hypochromic anemia, leukopenia, neutropenia, infections, diarrhea, neurologic disturbances, hypopigmentation of the skin and hair, and bony changes. Clinical conditions in adults that predispose to copper deficiency include total parenteral nutrition without copper supplementation, malabsorptive syndromes, gastrectomy, gastric bypass, and chronic biliary fistulas. Excess supplemental zinc or iron can decrease copper absorption. Toxicity from excess administration of oral copper includes acute hemorrhagic gastritis.

Phosphorus

Phosphorus deficiency is common in patients with malnutrition, malabsorptive disorders, and alcoholism and in refeeding syndrome. Cardiac failure, hemolytic anemia, rhabdomyolysis, acidosis, and encephalopathy may develop with phosphorus deficiency.

Miscellaneous Minerals

Deficiencies of selenium (cardiomyopathy and myositis), chromium (hyperglycemia and neurologic symptoms), manganese (very rare, with nonspecific features), or molybdenum (neurologic symptoms) may develop in patients receiving long-term total parenteral nutrition or tube feeding without proper supplementation. Manganese excess may occur in patients who are oversupplemented with parenteral nutrition; they may present with headache, vomiting, and parkinsonian-like symptoms due to the effects on the basal ganglia.

Bariatric Surgery

Metabolic complications should be anticipated after bariatric surgery. Protein malnutrition or zinc deficiency can cause hair loss. Deficiencies of vitamins D, A, E, and B_{12} and thiamine, folate, iron, and copper may occur if supplementation and monitoring are deficient.

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Questions and Answers

Abbreviations used:

ALT, alanine aminotransferase
AST, aspartate aminotransferase
EGD, esophagogastroduodenoscopy
HIV, human immunodeficiency virus
INR, international normalized ratio
MAI, *Mycobacterium avium-intracellulare* complex
MTE-4, multiple trace elements 4
PAS, periodic acid-Schiff
SIBO, small intestinal bacterial overgrowth
TPN, total parenteral nutrition

Multiple Choice (choose the best answer)

III.1. **A 67-year-old woman presents with a history of 4 months of diarrhea and bloating. She has 4 to 6 loose bowel movements daily, associated with a 4.5-kg weight loss. She also has noticed significant abdominal bloating. She has a past medical history of cervical cancer 5 years ago, for which she underwent hysterectomy, chemotherapy, and radiotherapy, and she is currently considered to be disease-free. On examination, she has a distended abdomen and an abdominal scar. On laboratory testing, she has a macrocytic anemia and a low serum B_{12} level. Her tissue transglutaminase level is normal. Abdominal imaging shows chronic radiation changes throughout the small bowel. Which of the following is most likely to be useful in managing this patient?**

a. Gluten-free diet
b. Antibiotics
c. Surgical resection
d. Prednisone
e. TPN

III.2. **A 72-year-old woman undergoes resection of 325 cm of small bowel for complications of acute mesenteric ischemia from an embolic source related to new atrial fibrillation. Otherwise, she has been healthy until now. She receives rate-control therapy with a β-blocker and is now in sinus rhythm. Within the first week after surgery, she complains of frequent, voluminous diarrhea. She has been receiving TPN and has begun to supplement with oral liquid intake. She has been taking high-dose loperamide and diphenoxylate with atropine, each taken 4 times daily. Which of the following is the next best step?**

a. Increase long-chain triglyceride intake
b. Add cholestyramine
c. Convert medications to elixirs
d. Increase oral free water intake
e. Add acid suppression

III.3. **A 29-year-old woman with known celiac disease presents for her annual follow-up. Celiac disease was diagnosed 2 years ago when she presented with iron-deficiency anemia. She states that she strictly adheres to her diet. She feels well and has no new complaints other than mild fatigue. In addition to celiac disease, she has a history of osteopenia and has been taking calcium and vitamin D replacement. Laboratory testing now shows a normal complete blood cell count, AST 147 U/L, ALT 153 U/L, and alkaline phosphatase 68 U/L, with normalization of her tissue transglutaminase antibodies, which were initially elevated. Her liver biochemistry results were normal at presentation 2 years ago. Right upper quadrant ultrasonography findings are normal. Which of the following is the next best step?**

a. Check serum 25-hydroxyvitamin D level
b. Schedule a consultation with a dietician
c. Check antimitochondrial antibody levels
d. Schedule magnetic resonance cholangiopancreatography
e. Check antinuclear and smooth muscle antibody levels

III.4. **A 37-year-old man presents with a history of diarrhea for 1 month. He has 6 to 8 loose bowel movements daily, including nocturnal stools, without blood or melena. He also notes**

progressive bilateral swelling of his legs and the development of a distended abdomen over the past few weeks associated with a 4.5-kg weight gain. He denies bloating or flatus. His past medical history is significant for Hodgkin lymphoma 8 years ago, for which he received mantle field irradiation. He has ascites on examination and significant lower extremity edema. Laboratory testing shows a normal complete blood cell count and electrolyte levels, serum albumin 2.1 g/dL (reference range, 3.5-5.0 g/dL), and total protein 4.0 g/dL (reference range, 6.0-8.5 g/dL). Prothrombin time/INR and 25-hydroxyvitamin D level are normal. Stool cultures, including an evaluation for *Clostridium difficile*, have been negative. An EGD and colonoscopy, both with biopsies, are unremarkable. Which of the following is the next best test?

a. An α_1-antitrypsin clearance test
b. Hydrogen breath testing
c. Polymerase chain reaction for Whipple disease
d. A 72-hour fecal fat collection
e. Congo red staining of intestinal biopsies

III.5. A 39-year-old man presents with diarrhea, fatigue, and a 9.1-kg weight loss over the past 6 months. He has a known history of HIV and has not adhered to medical follow-up. He denies fevers but has had night sweats. He also reports arthralgias. On examination, he appears thin and has palpable diffuse adenopathy. His CD4 cell count is 80/μL, but other laboratory results are unremarkable. Stool cultures are negative for enteric pathogens. He undergoes an upper endoscopy, where small-bowel biopsies show villous blunting, with no intraepithelial lymphocytosis, and a normal plasma cell population. PAS staining on the duodenal tissue is positive. Which is the next best step?

a. Polymerase chain reaction for *Tropheryma*
b. Acid-fast staining
c. Tissue transglutaminase antibody
d. Immunoglobulin levels
e. Anti-enterocyte antibodies

III.6. A 56-year-old man had a Whipple resection 5 days ago for an ampullary carcinoma with painless jaundice. Before surgery, he had no bowel complaints, with 2 formed bowel movements daily. He now reports having 5 to 7 loose bowel movements daily accompanied by excessive bloating. There has been no nocturnal awakening to have a bowel movement. His past medical history is gastroesophageal reflux and Barrett esophagus without dysplasia, for which he takes a proton pump inhibitor once daily for control of symptoms. For the past few days, he has had breakthrough reflux-type symptoms and has been given an antacid several times daily. Stool cultures in the hospital, including culturing for *Clostridium difficile*, have been negative. Stool sodium was 50 mmol/L, and stool potassium was 30 mmol/L. Which of the following is the most likely cause of his diarrhea?

a. *Clostridium difficile* infection
b. Proton pump inhibitor use
c. Bile acid–induced diarrhea
d. SIBO
e. Antacid use

III.7. A 52-year-old man complains of fatigue. Ten years ago, he underwent a gastrojejunal bypass for morbid obesity. In the first 2 years he lost 41 kg, and he has maintained his weight over the past 8 years. On physical examination, he appears well, but he has some gait ataxia. A complete blood cell count shows a microcytic, hypochromic anemia and mild leukopenia and neutropenia. Which of the following most likely explains this patient's symptoms and laboratory tests?

a. Elevated serum methylmalonic acid
b. Elevated serum homocysteine
c. Low serum ferritin
d. Low serum copper
e. Low serum methylmalonic acid

III.8. A 78-year-old woman with scleroderma complains of diarrhea and a 4.5-kg weight loss. She has been taking a proton pump inhibitor and eats well. Her hemoglobin is 10.8 g/dL with mean corpuscular volume of 103 fL. She denies drinking alcoholic beverages. Stool tests for infection are negative. Colonoscopy with ileoscopy and biopsies are normal. Results of a 48-hour stool collection while eating a high-fat diet are 302 mL daily, with 16 g of fat per 24 hours. Endoscopy with small-bowel biopsies shows mildly increased intraepithelial lymphocytes. Celiac serology is negative. Which of the following blood test scenarios is most likely?

a. Low vitamin B_{12}, high folate, high methylmalonic acid
b. Low vitamin B_{12}, low folate, high methylmalonic acid
c. Normal vitamin B_{12}, normal folate, normal methylmalonic acid
d. Normal vitamin B_{12}, low folate, normal methylmalonic acid
e. Low vitamin B_{12}, high folate, low methylmalonic acid

III.9. A 35-year-old man presents with a scaly, hyperpigmented rash involving his arms, hands, face, and neck. It is summer, and use of sunscreen did not improve his skin. He works outside at a restaurant where he ingests several beers each day. His diet is unbalanced. His stools have been loose, and he has poorly localized, crampy abdominal pain. Computed tomography of the abdomen shows an ileal mass worrisome for a tumor, with possible hepatic metastases. Which of the following best explains his presentation?

a. Riboflavin deficiency
b. Celiac disease
c. Coproporphyria
d. Carcinoid syndrome
e. Acute intermittent porphyria

III.10. A 26-year-old man with Wilson disease has a red, scaly rash around his mouth. He has been well for some time. He takes D-penicillamine. He also notes increased difficulty with night vision. Which of the following supplementations would most likely help him?

a. Pyridoxine
b. Copper
c. Zinc
d. Vitamin A
e. Riboflavin

III.11. A 28-year-old man with Crohn disease has begun receiving TPN. He has a history of colectomy, multiple small-bowel resections, and ileorectal anastomosis, with gradual loss of weight due to short bowel syndrome. He feels well. Laboratory tests 2 weeks after starting TPN show ALT 78 U/L, AST 59 U/L, and normal alkaline phosphatase, total bilirubin, creatinine, and complete blood cell count. The liver test abnormalities are new. Three weeks ago, before he began receiving TPN, he received 2 units of packed red blood cells. His wife has chronic hepatitis C. Which of the following is most likely to account for these new liver test abnormalities?

a. TPN
b. Blood transfusions
c. Crohn disease
d. Primary sclerosing cholangitis
e. Acute hepatitis C

III.12. A 62-year-old man is referred to you for fatigue, lower leg discomfort, and abnormal liver test results. Many years ago he had a substantial resection of his small bowel to treat incarcerated hernia, and he has been receiving home TPN for

many years. For several months, he has been fatigued, with discomfort in both calves. On physical examination, his calves are tender, and he has a third heart sound. Doppler ultrasonographic findings of both legs are unremarkable, with no thrombi. His complete blood cell count and alkaline phosphatase are normal, but his AST is 250 U/L. Which of the following most likely explains all of this?

a. Elevated creatine kinase
b. Hepatitis B surface antigen positivity
c. Low selenium
d. Elevated thyrotropin
e. Low chromium

Answers

III.1. Answer b.
This patient likely has SIBO, with the risk factor being radiation enteritis. The diarrhea, weight loss, bloating, and macrocytic anemia due to vitamin B_{12} deficiency are typical. Treatment of SIBO is antibiotic therapy, and patients may need subsequent or rotating courses of antibiotics depending on the frequency of recurrent symptoms. She is unlikely to have celiac disease with a normal tissue transglutaminase antibody level, so a gluten-free diet is not needed. Although she has radiation changes to the small bowel, surgical resection of the involved small bowel could lead to significant diarrhea and short bowel syndrome. While prednisone can be used in cases of inflammatory bowel disease, it will not help this patient with radiation enteritis. Similarly, the use of TPN is not needed when the patient is able to tolerate oral intake, and use of the intestinal tract is always preferred when feasible.

III.2. Answer e.
Early postoperative management for patients with shortened bowel includes aggressive treatment with antidiarrheal agents and TPN, as this patient is doing. In addition, gastric acid suppression is essential given that there is hypersecretion of gastric acid in the early postoperative period, which leads to pancreatic lipase inactivation, resulting in diarrhea and steatorrhea. Since this patient had more than 100 cm of small bowel resected and likely has bile salt deficiency, she will need to be considered for supplementation with medium-chain triglycerides (not long-chain), which do not require bile salts and micelle formation for absorption. Similarly, adding cholestyramine would not be recommended since it would bind the few remaining bile salts that are recirculating, worsening her diarrhea. Elixirs contain sorbitol and other sugar alcohols that can cause diarrhea from the increased osmotic load, so that would not be recommended at this time unless the patient could not take any oral pills. This patient should be taking oral rehydration solution and instructed in its use since it contains sodium and glucose to aid in fluid absorption; excess free water intake may actually worsen the diarrhea.

III.3. Answer e.
Celiac disease is associated with several hepatic conditions, including autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis. Some patients also have nonspecific liver findings with celiac disease related to gluten in the diet. This patient may very well have autoimmune hepatitis, the hepatic condition seen most commonly with celiac disease, given that she is eating a gluten-free diet and has a hepatitic pattern of injury. Antinuclear and smooth muscle antibody levels would be helpful to check next. Vitamin D deficiency (resulting in osteomalacia) would cause an isolated alkaline phosphatase elevation, which is not present. Since the patient states that she is adhering to her gluten-free diet and her tissue transglutaminase antibodies have normalized, there is no need to reconsult a dietician at this time. With no evidence of cholestasis, antimitochondrial antibodies and magnetic resonance cholangiopancreatography would not be necessary at this time.

III.4. Answer a.
This patient's diarrhea, ascites, and edema are likely secondary to a protein-losing enteropathy due to the effects of prior radiation on lymphatic drainage, causing a protein-rich fluid to be lost in the intestinal tract. An α_1-antitrypsin clearance test can be used to document the protein-losing state. While this patient may have concomitant carbohydrate malabsorption, the lack of bloating or excess flatus and the secretory nature of his diarrhea make breath testing less imperative as a next step. The normal small-bowel biopsy findings argue against a diagnosis of Whipple disease as a cause of his diarrhea. The patient does not have features of fat malabsorption given that he has not had weight loss or laboratory features of fat-soluble vitamin deficiencies, so a 72-hour fecal fat collection is not needed at this time. While amyloid can cause a protein-losing enteropathy (in which Congo red staining may be helpful), this patient has another more obvious reason to have a protein-losing state.

III.5. Answer b.
This patient is likely to be infected with MAI, given his history of HIV and significantly suppressed CD4 cell count. MAI causes small-bowel villous blunting, with PAS positivity. In addition, acid-fast staining will be positive and ought to be the next step in his care. Although Whipple disease can cause villous blunting and PAS-positive staining, the patient's risk is higher for MAI than for Whipple disease, and hence acid-fast staining is likely to be of higher yield. Tissue transglutaminase antibody would evaluate for celiac disease, and in addition to villous blunting, the small-bowel histology should have shown features of intraepithelial lymphocytosis and chronic inflammation, which were not seen. In cases of hypogammaglobulinemia, plasma cells would not have been noted in normal concentration. In patients with autoimmune enteritis, for which anti-enterocyte antibodies can be checked, the villi are often significantly atrophied, and this condition would be much less likely than MAI infection in this man.

III.6. Answer e.
This patient has new-onset diarrhea since being in the hospital. He is taking an antacid several times daily, and several antacids contain magnesium, which can cause an osmotically driven diarrhea. This diagnosis would be supported by the osmolar gap on stool studies based on the following calculation: 290 mOsm/kg – 2(50 + 30) = 130 mOsm/kg. A gap greater than 100 mOsm/kg supports an osmotic cause for the diarrhea. He was already checked once for *Clostridium difficile*, and the culture was negative, so that is unlikely to be the cause of his symptoms. Proton pump inhibitor use can cause secretory diarrhea and microscopic colitis but not an osmotically driven diarrhea. In cases of small-bowel resections or with biliary surgery, excess bile acids can irritate the colon and cause a secretory diarrhea, which this patient does not have. While this patient may be at risk for SIBO given his altered bowel anatomy, the symptoms would not occur this suddenly and this close to the timing of his surgery.

III.7. Answer d.
This patient most likely has a low copper level, with a hypochromic microcytic anemia, leukopenia, neutropenia, and neurologic disturbances, particularly gait ataxia. Vitamin B_{12} deficiency

(answer choices *a* and *b*) would not cause a hypochromic microcytic anemia, and iron deficiency (answer choice *c*) would not explain the neurologic findings.

III.8. Answer a.
This patient, with mild malabsorption, macrocytic anemia, and diarrhea, most likely has SIBO (with low vitamin B_{12}, high folate, and high methylmalonic acid), on the basis of stasis (scleroderma), proton pump inhibitor therapy, and her age.

III.9. Answer d.
The rash suggests pellagra due to niacin deficiency. The most likely cause is carcinoid syndrome, which, for a person consuming an unbalanced diet and drinking several beers daily, might very well increase the risk of pellagra. Riboflavin deficiency would not explain any of this. The rash seen with celiac disease (dermatitis herpetiformis) is pruritic and found on extensor surfaces. There is no rash with acute intermittent porphyria, and the rash in coproporphyria would not be scaly and hyperpigmented. Neither porphyria would include an ileal mass lesion or hepatic metastases.

III.10. Answer c.
The patient's rash could be due to zinc deficiency and might be similar to the seborrheic dermatitis seen with pyridoxine or riboflavin deficiency. Night blindness could be due to vitamin A or zinc deficiency. Thus, zinc supplementation for zinc deficiency, which can occur with chronic chelation therapy with D-penicillamine, is the best answer. One would not give copper supplements to a patient with Wilson disease.

III.11. Answer a.
TPN and overfeeding may cause mildly elevated ALT and AST levels, which improve over time. Viral hepatitis from a blood transfusion is unlikely given the low risk of infected donor blood and the short interval (3 weeks) between transfusion and the ALT elevation. There is no reason why the patient's Crohn disease would flare now, and he feels well. Patients who have primary sclerosing cholangitis usually present with cholestatic liver test abnormalities. Acute hepatitis C from sexual transmission from his wife is also unlikely (long-term risk is about 5% in monogamous relationships in which 1 person has hepatitis C).

III.12. Answer c.
This patient most likely has myalgias due to selenium deficiency, not an uncommon problem in persons receiving prolonged home TPN who receive trace elements without selenium (such as MTE-4 supplementation). Although an elevated creatine kinase level can occur in myositis, it would not explain this patient's full presentation with the cardiac finding and the leg discomfort. His elevated AST is probably from muscle, not liver, so hepatitis B is less likely. Although thyroid insufficiency is common, it is less likely to cause isolated myalgias. Chromium deficiency causes diabetes mellitus and would not account for this presentation.

IV

Miscellaneous Disorders

10

Gastrointestinal Manifestations of Human Immunodeficiency Virus Infection

STEPHEN C. HAUSER, MD

Nearly 70 million people worldwide have been infected with human immunodeficiency virus (HIV) type 1, and more than 35 million have died of complications from the infection. More than 1 million persons in the United States have been infected with HIV. Highly active antiretroviral therapies (HAARTs) with multiple drugs—now widely used in the United States and highly effective—have greatly diminished the incidence of opportunistic infections in patients infected with HIV.

Suppression of the viral load to less than 50 copies/mL and maintenance of adequate CD4 lymphocyte counts (>500/μL) are crucial. Opportunistic infections and malignancies are uncommon in HIV-infected patients with plasma HIV viral loads less than 10,000 copies/mL and CD4 cell counts greater than 200 to 500/μL. However, not all patients with HIV infection receive adequate therapy because of factors related to cost, adherence to therapy, lack of availability of treatment in certain parts of the world, drug resistance, drug toxicity, and drug-drug and drug–alternative substance interactions. Also, in up to 25% of persons in the United States infected with HIV, the infection is undiagnosed.

In immunosuppressed HIV-infected patients, multiple infections often occur simultaneously. Presentations may be typical or atypical, and there is great overlap in clinical signs and symptoms between infections and malignancies. In patients with successfully treated HIV infection, gastrointestinal tract disorders are more likely to be similar to those in persons without HIV infection and otherwise healthy persons (eg, dysphagia due to gastroesophageal reflux disease rather than an opportunistic infection). Opportunistic infections that previously were difficult to treat in immunosuppressed HIV-infected patients (ie, *Cryptosporidium* and Microsporida infections) may resolve with successful HAART.

Adverse effects of antiretroviral therapy involving the gastrointestinal tract (and liver) are common and need to be considered in patients who have common complaints and disorders such as anorexia, nausea, vomiting, oral ulcers, abdominal pain, diarrhea, pancreatitis, or liver function test abnormalities.

- Successful antiretroviral drug therapy has diminished greatly the incidence of opportunistic infections in patients infected with HIV.
- Multiple infections often occur simultaneously in immunosuppressed HIV-infected patients.
- Adverse effects of antiretroviral drug therapy involving the gastrointestinal tract are common.

Oral Cavity

Oral lesions occur in up to 80% of HIV-infected patients and may be the first symptom in up to 10% of patients (Table 10.1).

Esophagus

Case

A 27-year-old man who has HIV infection presents with new dysphagia to solids. He is an injection drug user and has been nonadherent with antiretroviral drug therapy. Thrush is found on physical examination. The CD4 cell count is 110/μL, and his plasma HIV viral load is more than 30,000 copies/mL.

The clinical presentation of this patient strongly suggests an opportunistic infection of the esophagus with *Candida*, and initial treatment should focus on the HIV infection and empirical administration of fluconazole.

Abbreviations: CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HSV, herpes simplex virus

Table 10.1. Oral Lesions in HIV-Infected Patients

Agent or Condition	*Features*	*Treatment*
Candidiasis (usually *Candida albicans*; other *Candida* species may be resistant to azoles)	With or without pain: pseudomembranous (thrush), erythematous (atrophic), hyperplastic (painless, white; does not rub off)	Topical nystatin, clotrimazole or systemic fluconazole, or itraconazole
	Culture, KOH, Gram stain, rarely biopsy	
Cryptococcus, histoplasmosis, geotrichosis, *Penicillium marneffei* (Asia), *Leishmania*	Painful, nodular, ulcerated; rare	Antifungals
Oral hairy leukoplakia (Epstein-Barr virus)	Painless, often on tongue, not red, does not peel off	If symptomatic, high-dose acyclovir or ganciclovir
	Biopsy, viral studies	
Herpes simplex virus	Biopsy, Tzanck preparation	Acyclovir, famciclovir, or valacyclovir
		If resistance, foscarnet or cidofovir
Herpes zoster	Rare	Antivirals
Cytomegalovirus	Rare	Ganciclovir, foscarnet, or cidofovir
Oral condylomata	Human papillomavirus	
Aphthous ulcers	Painful; no organisms in biopsy specimen	Topical anesthetics, dexamethasone, systemic corticosteroids, or thalidomide
	Possibly HIV induced	
Bacillary angiomatosis	*Bartonella henselae* or *Bartonella quintana*; papules or ulcers	
	Biopsy	
Syphilis	Rare	
Lymphomatoid granulomatosis	Rare	
Granuloma annular	Rare	
Mycobacterium avium-intracellulare complex	Rare	
Non-Hodgkin lymphoma		
Kaposi sarcoma		
Squamous cell carcinoma		
Necrotizing gingivitis and periodontitis		

Abbreviations: HIV, human immunodeficiency virus; KOH, potassium hydroxide.

Esophageal Disorders

Common symptoms of esophageal disorders include dysphagia, odynophagia, and chest pain unrelated to swallowing. With successful antiretroviral treatment of HIV infection, common disorders such as gastroesophageal reflux disease and pill esophagitis are more likely to occur than infectious esophagitis. Of the opportunistic infections involving the esophagus, the most common fungal infection is caused by *Candida* and the most common viral infection is caused by cytomegalovirus (CMV); herpes simplex virus (HSV) infection is less common. *Candida* infection often causes dysphagia, whereas CMV and HSV infections and idiopathic esophageal ulceration often cause odynophagia. Two-thirds of patients with *Candida* esophagitis have oral thrush, so empirical therapy has a role; however, nearly 25% have a second cause of their symptoms (multiple coexistent pathogens). CMV infection and idiopathic esophageal ulceration are unusual if the CD4 cell count is more than 100/μL.

Empirical treatment with fluconazole is recommended for patients with mild to moderate symptoms (dysphagia or odynophagia) who have thrush. About 75% have a response in 3 to 5 days to a 200-mg loading dose on the first day, followed by 100 mg daily for 14 to 21 days. Endoscopy is indicated for patients who do not have a prompt response to treatment or who are severely symptomatic. Barium studies are not useful. At endoscopy, brush cytology is more sensitive than biopsy to diagnose *Candida* esophagitis, although the typical appearance is very specific (multiple plaquelike, often linear or confluent creamy-white lesions, with bleeding points when removed). *Candida* often is an oral commensal (in up to 50% of cases) and usually is found in stool specimens (in up to 90% of cases). Also, patients with *Candida* esophagitis can be asymptomatic. Treatment may be topical for mild cases. Ketoconazole and itraconazole absorption are dependent on acid in the stomach. Some patients with *Candida* esophagitis may not have a response to fluconazole. Voriconazole, posaconazole, anidulafungin, caspofungin, or micafungin also may be effective. Amphotericin compounds are used less often now than previously. Only rare cases with frequent, severe recurrences merit fluconazole (100-200 mg daily) for secondary prophylaxis. Primary prevention is not recommended.

CMV infection often produces large, but sometimes small, shallow or deep, focal or serpiginous, usually painful (odynophagia or chest pain) ulcers in the middle to distal third of the esophagus. Erosions, strictures, fistulas, perforations, or mass lesions are less frequent. Up to 15% of persons with CMV esophagitis have concomitant retinitis; thus, a complete ophthalmologic examination should be performed. The diagnosis of CMV esophagitis requires endoscopy, with biopsy specimens taken from the base of the ulcer (CMV involves the vessels and endothelium, whereas HSV affects epithelial cells at the edge of ulcers) to examine for cytopathic effects (intranuclear inclusions, perinuclear halo, and cytoplasmic inclusions). Serologic studies (most patients are already positive) and culture studies (contamination with blood) are less specific. Immunohistochemistry and in situ hybridization can improve sensitivity. Treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, as well as HAART, usually helps.

Patients with HSV esophagitis often present with multiple small, superficial ulcers ("volcano" ulcers) or erosive esophagitis (Figure 10.1). Strictures and fistulas are rare. Vesicles rarely are visualized. Biopsy specimens from the edge of ulcerations should show cytopathic changes (ground-glass nuclei, eosinophilic Cowdry type A intranuclear inclusions, and multinucleate cells). Treatment with acyclovir or foscarnet usually is successful. Primary prophylaxis is not recommended. Some patients with frequent, severe recurrences require secondary prophylaxis.

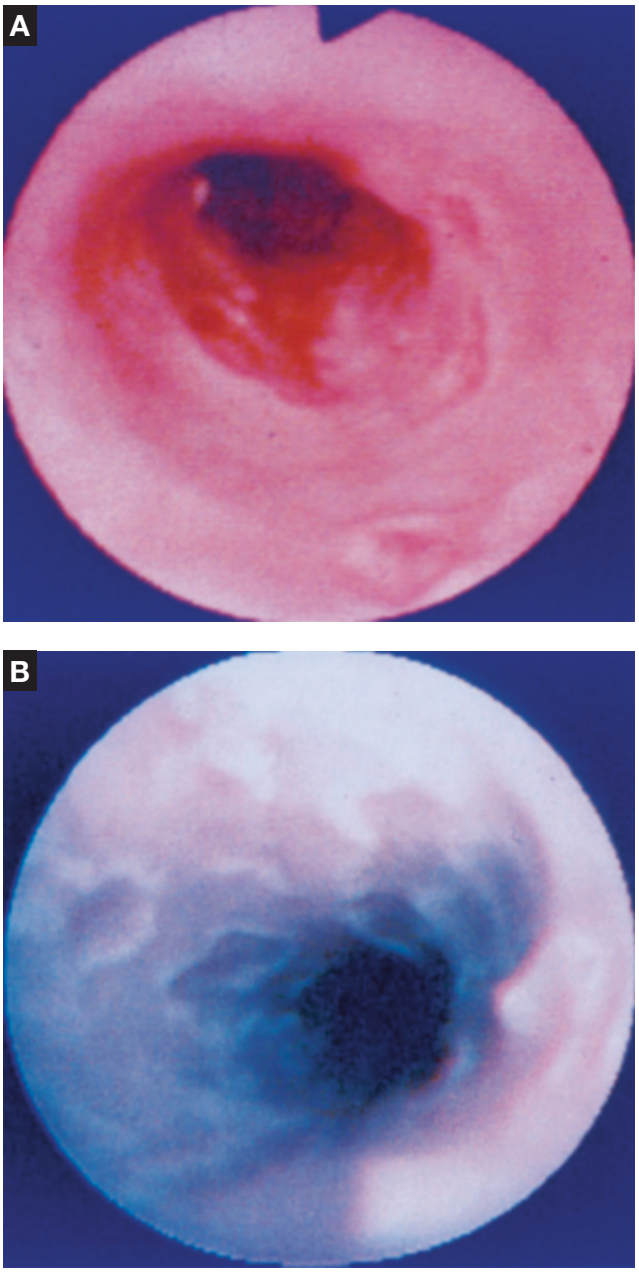

Figure 10.1. Herpes Simplex Esophagitis. Endoscopic photographs of herpes simplex esophagitis show multiple superficial ulcers. A, Distal esophagus. B, Midesophagus. (Adapted from Treadwell TL, Peppercorn MA, Koff RS. The gastroenterology teaching project unit 6—gastrointestinal infections and AIDS. Used with permission.)

Idiopathic esophageal ulcers may be single or multiple, and they often occur in the distal esophagus. By definition, all diagnostic studies (biopsy, brush, cultures, and special studies) are negative. Pain is the norm, and fistulas may occur. Treatment includes corticosteroids or thalidomide.

Other unusual causes of esophageal lesions include infections with papillomavirus, Epstein-Barr virus, papovavirus, *Histoplasma, Aspergillus*, Mucorales, *Cryptococcus, Actinomyces, Nocardia, Leishmania, Cryptosporidium, Pneumocystis, Mycobacterium tuberculosis*, and *Mycobacterium avium-intracellulare* complex as well as bacillary angiomatosis, lymphomatoid granulomatosis, non-Hodgkin lymphoma, and Kaposi sarcoma.

- Infections caused by *Candida* and CMV are the most common opportunistic infections of the esophagus.
- Cytopathic changes diagnostic of CMV or HSV ulceration involving the esophagus are found most often in biopsy specimens from the base (CMV) or edge (HSV) of the ulceration.

Stomach

Gastric disorders related to immunosuppression of persons infected with HIV are uncommon. Epigastric discomfort may be due to CMV infection involving the stomach or, more likely, gastroesophageal reflux disease, distal esophageal ulceration (due to CMV infection, idiopathic esophageal ulceration, or HSV infection), peptic ulcer disease, or dyspepsia. Patients with gastric lymphoma can present with anorexia, nausea, vomiting, pain, or bleeding, whereas patients with Kaposi sarcoma involving the stomach are more likely to be asymptomatic. Whether "AIDS gastropathy" (achlorhydria or hypochlorhydria with gastric atrophy and antiparietal cell antibodies) exists is unclear. Rare infections of the stomach include cryptosporidiosis, histoplasmosis, bacillary angiomatosis, herpes zoster, leishmaniasis, syphilis, and infection with *M avium-intracellulare* complex. Also, idiopathic aphthous ulcers have been identified in the stomach.

Small Bowel

Case

A 35-year-old woman with HIV infection treated successfully with antiretroviral drugs presents with voluminous watery diarrhea after a trip to Haiti. She complains of nausea, cramps, and a recent 2.3-kg weight loss, but she states that she does not have fever or gastrointestinal tract bleeding. Fecal leukocytes and occult blood are not observed on stool examination. Standard stool cultures for bacteria are negative. Mild eosinophilia is apparent on a peripheral blood smear.

The clinical presentation of this patient is consistent with *Cystoisospora belli* infection of the small bowel, which is endemic in Haiti. This should respond promptly to antibiotic treatment with trimethoprim-sulfamethoxazole. Because antiretroviral drug therapy has been successful in this patient, recurrent infection is not likely.

Small-Bowel Disease

The principal presentation of small-bowel disease in HIV-infected patients is enteritis, with diarrhea that is often high volume, watery, and fecal-leukocyte negative and sometimes with nausea, vomiting, bloating, periumbilical cramps, weight loss, or malabsorption. Diarrhea of colonic origin is more likely to be small volume, with frequent, urgent, loose stools, and lower abdominal pain and is often fecal-leukocyte positive, with or without blood. Opportunistic infections are more likely to occur in persons with CD4 lymphocyte counts less than 100 to 200/μL. Commonly, medications used to treat HIV infection, most often protease inhibitors (especially ritonavir), are implicated as a cause of diarrhea. In diarrhea thought to be due to infection, a pathogen is identified in only 50% to 85% of cases and more than 1 pathogen may be discovered in up to 25% of cases.

The initial diagnostic approach to chronic diarrhea in HIV-infected patients should include the following: 1) freshly collected stools for bacterial culture (including *Salmonella, Campylobacter*, and *Shigella*), ova and parasites, fecal leukocytes, and *Clostridium difficile* toxin; 2) special

studies (monoclonal antibodies, modified acid-fast and trichrome stains) for *Giardia, Cryptosporidium, Cyclospora*, and Microsporida; and 3) blood cultures for enteric pathogens and *M avium-intracellulare* complex (especially if the patient is febrile). If the results of these studies are negative, especially in sicker and more immunosuppressed patients, endoscopic evaluation is indicated. Persons who are less ill and have a CD4 lymphocyte count greater than 200/μL and no pronounced weight loss usually do not have an opportunistic infection and can be given an empirical trial of antidiarrheal medications. Endoscopy with small-bowel (preferably distal duodenum or proximal jejunum) biopsy and aspiration for parasites can be performed when a small-bowel source for the diarrhea is suspected. Colonoscopy with ileoscopy and ileal biopsy can be helpful in the detection of selected small-bowel infections (*Cryptosporidium*).

Small-Bowel Infections

Small-bowel infections are caused by several agents.

Cryptosporidium. *Cryptosporidium*, a ubiquitous parasite, causes a zoonosis (from cats, dogs, calves, lambs, and other animals, especially newborn pets) and is transmitted by the fecal-oral route (including human sources) and, worldwide, through contamination of food (raw oysters and unpasteurized juices) and water (including recreational water) by as few as 10 to 100 oocysts. It usually infects small-bowel epithelial cells (apical, small [2-8 μm], extracytoplasmic but intracellular sporozoites), with various degrees of villous atrophy, but it also can involve the esophagus, stomach, colon, biliary tree, or lung. Diagnosis can be made by examining the stool for oocysts (modified acid-fast stain or enzyme-linked immunosorbent assay) or performing biopsy of the small bowel (biopsy of the terminal ileum may be more helpful diagnostically than biopsy of the proximal small bowel). Rectal biopsy findings also may be diagnostic. Severe high-volume diarrhea with wasting (malabsorption, lactose intolerance, or vitamin B_{12} deficiency) is most common when CD4 cell counts are less than 50/μL. Specific therapy with medications such as paromomycin, nitazoxanide, and azithromycin can be helpful, but antiretroviral therapy has the best chance of improving the diarrhea.

Microsporida. Diseases from 2 species of fungi (formerly classified as parasites) in the order Microsporida, *Enterocytozoon bieneusi* and *Encephalitozoon* (*Septata*) *intestinalis*, can be transmitted as a zoonosis or by the fecal-oral route. Most often, infection occurs in patients with CD4 cell counts less than 100/μL. Ingestion of watermelon can be a risk factor. *Enterocytozoon bieneusi* involves small-bowel epithelium (small-bowel biopsy, intracellular, 1- to 2-mm meronts and spores [Figure 10.2]) or the hepatobiliary tree. *Encephalitozoon intestinalis* involves intestinal and often extraintestinal sites (kidney or lung). Currently, the diagnosis usually can be made with stool examination (modified trichrome stain, chemofluorescent agents, or monoclonal antibody testing) or with small-bowel biopsy (villous atrophy may be seen) or aspiration. The clinical presentation of immunosuppressed HIV-infected patients is similar to that of patients infected with *Cryptosporidium*. No effective antibiotic therapy is available for *Enterocytozoon bieneusi* infection. HAART is more likely to be helpful. The less common *Encephalitozoon intestinalis* infection can be treated with albendazole; *Encephalitozoon intestinalis* may be identified in the lamina propria of the small intestine and in urine sediment.

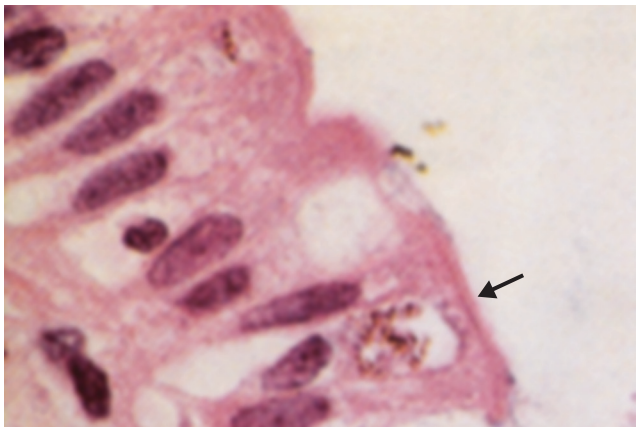

Figure 10.2. Microsporidial Spores. Small-intestinal biopsy specimen has a cluster of microsporidial spores within apical cytoplasm (arrow) (hematoxylin-eosin, original magnification ×350). (Adapted from Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises: Case 51-1993: a 36-year-old man with AIDS, increase in chronic diarrhea, and intermittent fever and chills. N Engl J Med. 1993 Dec 23;329[26]:1946-54. Used with permission.)

Cystoisospora belli. *Cystoisospora* (formerly *Isospora) belli* is another protozoan that is transmitted among humans by fecal-oral routes and contaminated water. It is endemic in developing countries (Haiti and Africa). Multiple large intracellular forms (schizonts, merozoites, and gametocytes), mild villous atrophy, and infiltrating eosinophils can be identified in small-bowel biopsy specimens, and stool examination (modified acid-fast stain) may show large oocysts and Charcot-Leyden crystals. Eosinophilia can be observed in peripheral blood smears. Infection with this parasite is treated with sulfonamides such as trimethoprim-sulfamethoxazole or with ciprofloxacin. Pyrimethamine in combination with leucovorin also has been used. However, recurrences are common in immunosuppressed patients and may require repeated courses of therapy or secondary prophylaxis, which also can include pyrimethamine in combination with sulfadoxine.

Cyclospora. The parasite *Cyclospora* is larger than *Cryptosporidium* but smaller than *Cystoisospora*. The species that infects humans, *Cyclospora cayetanensis*, is transmitted through fecal-oral routes and contaminated water, herbs (Thai basil), lettuce, snow peas, and fruit (especially raspberries). Diagnosis can be made with stool examination (acid-fast stains) or small-bowel biopsy (various degrees of villous atrophy are seen in biopsy specimens). As in *Cystoisospora* infection, trimethoprim-sulfamethoxazole or ciprofloxacin therapy is effective, but relapse may be frequent and require re-treatment or secondary prophylaxis.

Giardia *and* Entamoeba. *Giardia intestinalis* and *Entamoeba histolytica* infections are not more common, severe, or prolonged in HIV-infected patients than in patients who are not infected with HIV; however, infections are more common in those who practice oral-anal sex. *Entamoeba histolytica* has been found more often in HIV-infected persons in Taiwan than in HIV-infected persons elsewhere. Stool examination (for cysts and

trophozoites), duodenal aspirates, and stool antigen tests are used to make the diagnosis. Treatment is with metronidazole, tinidazole, or nitazoxanide.

Cytomegalovirus. Infection with CMV can occur throughout the gastrointestinal tract but is most common in the esophagus and colon. A diagnosis of any extraocular CMV infection mandates an ophthalmologic evaluation for concomitant CMV retinitis.

Mycobacterium. *Mycobacterium avium-intracellulare* complex can involve the small bowel. Patchy areas of edema, erythema, friability, erosions, nodularity, a frosted appearance, or yellowish nodules or plaques may be found at endoscopy. Patients with this infection usually have low CD4 lymphocyte counts (<100/μL) and often have fever, weight loss, night sweats, diarrhea, abdominal pain, anemia, and malabsorption. Ingestion of poorly cooked fish or shellfish and use of indoor swimming pools may increase the risk of exposure to and infection with this ubiquitous organism found in soil and water. Small-bowel biopsy specimens typically show macrophages stuffed with many acid-fast organisms. Blood cultures also may be diagnostic, but stool cultures do not accurately predict tissue-invasive disease. Culture results are required for differentiation from *M tuberculosis*, which, when present, usually affects the ileocecal region. Patients with mycobacterial infections may have extensive and bulky mesenteric or retroperitoneal adenopathy, with areas of central necrosis seen on computed tomography (Figure 10.3). Multidrug therapeutic regimens improve symptoms, and HAART ultimately can clear this systemic infection.

Uncommon Infections. Uncommon infections that may involve the small intestine include leishmaniasis, toxoplasmosis, *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) infection, histoplasmosis, candidiasis, coccidioidomycosis, aspergillosis, cryptococcosis, mucormycosis, and strongyloidiasis. Intestinal involvement with Kaposi sarcoma, often related to human herpesvirus 8 (purplish red submucosal lesions and frequently difficult to diagnose with endoscopic biopsy), is usually asymptomatic, but some of the lesions can hemorrhage. Recent reports suggest that saliva is an infectious source. Non-Hodgkin lymphoma often involves the small intestine and frequently is associated with fever, weight loss, abdominal pain, mass lesions, bleeding, and diarrhea. Most of these cases of lymphoma are of B-cell origin.

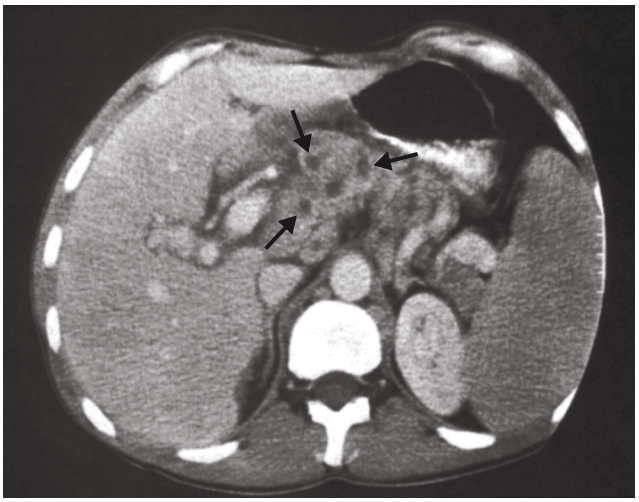

Figure 10.3. Mycobacterial Infection. Abdominal computed tomogram shows punctate areas of central necrosis within enlarged celiac and peripancreatic lymph nodes (arrows). (Adapted from Jeffrey RB Jr. Abdominal imaging in AIDS. Curr Probl Diagn Radiol. 1988;17:109-17. Used with permission.)

- Small-bowel disease often can be distinguished from large-bowel disease on the basis of clinical presentation.
- Medications used to treat HIV infection commonly cause gastrointestinal symptoms.
- Patients who are less ill, have CD4 cell counts greater than 200/μL, and do not have pronounced weight loss usually do not have opportunistic infections and can be given an empirical trial of antidiarrheal medications.

Colon

Case

A 32-year-old man who recently was found to be infected with HIV comes to the emergency department with new fever, abdominal pain, and bloody diarrhea. He recently bought his daughter a puppy at the local mall. The puppy has had nonbloody diarrhea.

The clinical presentation of this patient is consistent with colitis due to *Campylobacter* infection acquired from the infected puppy and emphasizes the importance of preventing exposure in HIV-infected persons.

Colon Disease

Diarrhea due to colon disease is extremely common in HIV-infected patients. Immunosuppressed patients are more likely to have enteric infections from *Salmonella, Shigella*, or *Campylobacter*. These infections, some of which also can involve the small bowel, tend to be more common, more persistent, more often resistant to antibiotics, and more likely to recur. In general, antibiotics such as ciprofloxacin are indicated for all HIV-positive immunosuppressed patients with *Salmonella* or *Shigella* infections, and in all but the most mild and self-limited *Campylobacter* infections. Empirical treatment with ciprofloxacin may be useful for presumed bacterial infections before the agent is identified. Blood cultures and stool examination for fecal leukocytes often are positive, especially for *Salmonella enteritidis* and *Salmonella typhimurium*. Another bacterial infection more common in HIV-infected patients is enteroaggregative *Escherichia coli. Yersinia, Aeromonas, Plesiomonas,* and other *E coli* may occur in these patients. *Streptococcus bovis* sepsis and endocarditis may be associated with gastrointestinal tract abnormalities such as colon cancer.

Exposure to the following should be avoided: raw shellfish (*Vibrio vulnificus*); reptiles (*Salmonella*); young or sick pets (*Salmonella, Campylobacter*, and *Cryptosporidium*); raw or undercooked eggs, meat, and shellfish (*Salmonella, Listeria*, noncholera vibrios, and *E coli* O157:H7); unpasteurized dairy products, poorly washed produce, soft cheeses, ready-to-eat cold cuts or hot dogs (*Listeria* and *Salmonella*); raw seed sprouts, refrigerated meat spreads, and deli foods that cannot be reheated; and unpasteurized apple cider (*E coli* O157:H7).

HIV-infected patients should also avoid the following: human and animal feces, contaminated water (drinking and recreational), newborn and very young pets, calves, lambs, reptiles, stray pets, contaminated soil, raw meat, raw fish, raw shellfish, travel to

parts of the world with probable exposure to unsafe food or water, unpasteurized juices, raw seed sprouts, questionable cold cuts, unclean produce, soft cheeses (eg, Brie, Camembert, feta, and blue-veined and Mexican-style cheese such as queso fresco), refrigerated pâtés, refrigerated meat spreads, poorly cooked eggs, poorly cooked and reheated leftovers, many deli foods, and food from street vendors.

CMV infection often affects the colon, with diarrhea, abdominal pain, bleeding, ulceration (Figure 10.4), mass lesion, perforation, fistula, low-grade fever, and weight loss as clinical manifestations. The CD4 lymphocyte counts usually are low (<50-100/μL). Infection may be asymptomatic. Diagnosis requires tissue biopsy specimens showing cytopathic changes; biopsy specimens from even normal-appearing areas can be diagnostic and should be taken. Use of immunohistochemistry increases the diagnostic yield. Also, CMV DNA testing of blood, tissue, and body fluids may be helpful. Up to 18% of cases may involve the right colon alone, and the infection would not be diagnosed with flexible sigmoidoscopy. Antiviral therapy with agents such as ganciclovir, foscarnet, or cidofovir usually is indicated, as well as HAART. Indications for use of the oral agent valganciclovir are to be determined.

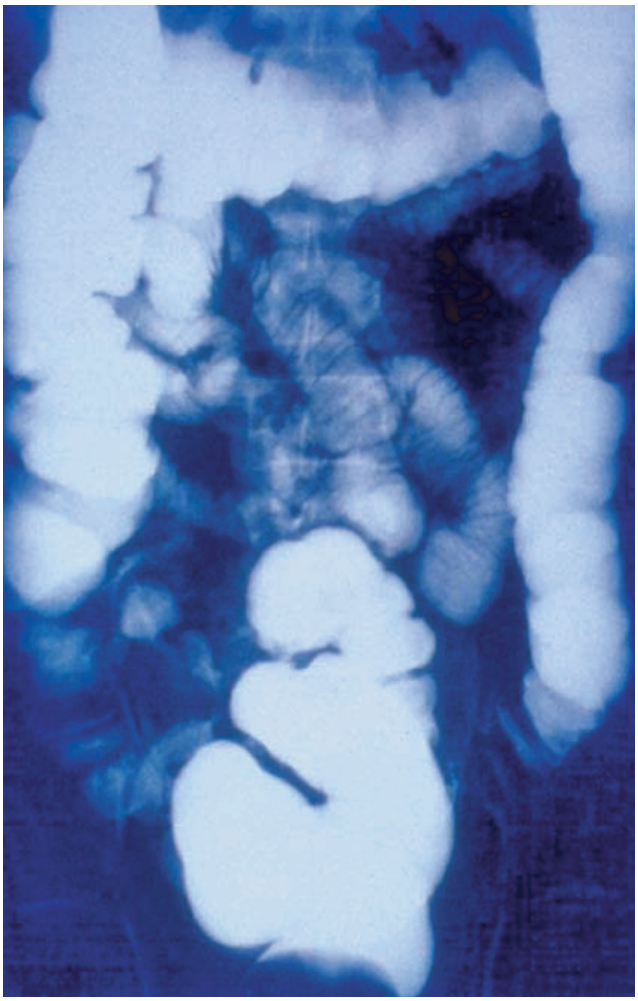

Figure 10.4. Cytomegalovirus Colitis. Barium enema shows cytomegalovirus colitis. Note mucosal edema, ulcerations, and narrowing of the transverse colon. These findings are nonspecific and can occur in other infections as well as in ischemic colitis. (Adapted from Treadwell TL, Peppercorn MA, Koff RS. The gastroenterology teaching project unit 6—gastrointestinal infections and AIDS. Used with permission.)

Clostridium difficile infection is the most common cause of bacterial diarrhea in the United States in HIV-infected persons. It is more common and more likely to be recurrent in immunosuppressed patients than in nonimmunosuppressed patients. Other less common infections are due to *M avium-intracellulare* complex, *M tuberculosis, Bartonella henselae* (bacillary angiomatosis), *Cryptosporidium, Entamoeba histolytica* (symptomatic colitis is rare), *Cryptococcus, Toxoplasma, Pneumocystis, Leishmania, Penicillium marneffei* (Southeast Asia), and *Candida*. Histoplasmosis and schistosomiasis are also less common than *C difficile* infections.

Several organisms found in stool samples are of uncertain clinical significance, including *Entamoeba* other than *Entamoeba histolytica, Balantidium coli*, spirochetes, *Blastocystis hominis*, adenovirus, *Rotavirus, Astrovirus, Coronavirus, Picobirnavirus*, and *Calicivirus*.

Other processes may occur, including lymphoma, Kaposi sarcoma, toxic megacolon (bacterial infections; CMV, *C difficile*, or *Cryptosporidium* infections; and Kaposi sarcoma related), typhlitis (sometimes without neutropenia), pneumatosis cystoides intestinalis (often associated with infections from agents such as CMV, *C difficile, Cryptosporidium*, and *M avium-intracellulare* complex), idiopathic colonic ulcer, and intussusception (due to infections, neoplasms, or lymphoid hyperplasia). Anorectal disease is more common in HIV-infected men who have sex with men than in other HIV-infected patients. These patients are at increased risk for herpes simplex infection (chronic cutaneous perianal ulcers, pain, tenesmus, mucopurulent discharge, inguinal lymphadenopathy, dysuria, and saddle paresthesias), CMV infection, gonorrhea, syphilis, idiopathic ulcer, condylomata (human papillomavirus), molluscum contagiosum, anal squamous cell carcinoma (especially with HIV and human papillomavirus coinfection), *Chlamydia* (lymphogranuloma venereum, serovars L1-L3) as well as *Actinomyces* infection, Kaposi sarcoma, lymphoma, and *Leishmania* infection.

- Many infections in immunocompromised HIV-infected patients can be prevented.
- Enteric infections may be diagnosed with blood culture and stool studies.
- Noninfectious causes of diarrhea have become more common in HIV-infected patients receiving antiretroviral medications.

Pancreas

Pancreatic involvement in immunosuppressed HIV-infected patients often results from medications and infections (pancreatitis) and less often from malignancy. Hyperamylasemia, pancreatic in origin or due to renal failure or macroamylasemia, may occur in asymptomatic persons. Medications often implicated in pancreatitis include dideoxycytidine, didanosine, pentamidine, dapsone, and trimethoprim-sulfamethoxazole. Infections and agents reported to involve the pancreas are protean and include CMV, herpes simplex virus, *Toxoplasma, Pneumocystis, Candida, Cryptococcus*, cryptosporidium, microsporidia, histoplasmosis, aspergillosis, *M avium-intracellulare* complex, and *M tuberculosis*. Kaposi sarcoma and lymphoma also may affect the pancreas.

Suggested Reading

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11

Nonvariceal Gastrointestinal Tract Bleeding[a]

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Upper Gastrointestinal Tract Bleeding

Introduction

Upper gastrointestinal (UGI) tract bleeding ("UGI bleeding") constitutes 75% to 80% of all cases of acute gastrointestinal tract bleeding. The incidence has decreased significantly; however, the mortality rate from acute UGI bleeding has decreased minimally in the past 50 years, ranging from 2.5% to 10%. This lack of change in mortality rate likely is related to the older age of patients who present with UGI bleeding and the increase in associated comorbid conditions. Peptic ulcers are the most common source of UGI bleeding, accounting for about 40% of cases. Other major causes are gastric erosions (15%-25% of cases), bleeding varices (5%-30%), and Mallory-Weiss tears (5%-15%). The use of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) is prevalent in 45% to 60% of all cases of acute bleeding. Moreover, the risk of UGI bleeding is increased in patients who take as few as 1 "baby" aspirin (81 mg) daily.

Initial Approach to Patients With UGI Bleeding

The initial evaluation of a patient with UGI bleeding should focus on assessment of 1) hemodynamic status and 2) comorbid conditions.

Melena can result when as little as 100 mL of blood is instilled into the UGI tract, and instillation of 1,000 mL or more initially leads to hematochezia. Hematochezia from UGI bleeding is a sign of significant bleeding and, if associated with a red nasogastric aspirate, has a mortality rate near 30%. Patients still bleed whole blood; therefore, the hematocrit may not decrease immediately with acute bleeding. Extravascular fluid will enter the vascular space and restore volume for up to 72 hours, thereby leading to a subsequent decrease in the hematocrit. Similarly, the hematocrit may continue to decrease for a few days after bleeding has stopped, and a decrease in hematocrit without clinical evidence of blood loss is not diagnostic of recurrent bleeding. Adequate intravenous access should be provided. Volume and blood resuscitation and stabilization of any other comorbid active medical conditions should be achieved before endoscopy. Rarely, massive bleeding cannot be stabilized adequately before endoscopy. Intubation for airway protection should be considered in patients with ongoing hematemesis or those with suspected active bleeding and decreased consciousness or loss of the gag reflex. There is no evidence that nasogastric lavage helps stop bleeding, although it may be helpful in cleansing the stomach before endoscopy.

Prognostic Factors

Clinical

Age older than 70 years is a risk factor for death from UGI bleeding. Comorbid conditions that increase mortality include pulmonary disease (acute respiratory failure, pneumonia, and symptomatic chronic obstructive pulmonary disease), malignancy, liver disorders (cirrhosis and alcoholic hepatitis), neurologic disorders (delirium and recent stroke), sepsis, postoperative state, and possibly cardiac disease (congestive heart failure,

[a] Portions of the Portal Hypertensive Gastropathy, Aortoenteric Fistula, Hematobilia and Hemosuccus Pancreaticus, and Vascular Anomalies sections have been published in Singh V, Alexander JA. The evaluation and management of obscure and occult gastrointestinal bleeding. Abdom Imaging. 2009 May-Jun;34(3):311-9. Used with permission.

Abbreviations: CREST, calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; H_2, histamine$_2$; NSAID, nonsteroidal antiinflammatory drug; UGI, upper gastrointestinal

ischemic heart disease, and dysrhythmia) and renal disorders (acute renal failure, creatinine >4 mg/dL, and dialysis). Signs of large-volume bleeding include fresh hematemesis or bright red nasogastric aspirate and shock, the 2 most predictive risk factors for death from UGI bleeding. Tachycardia (heart rate >100 beats per minute), orthostasis, and hypotension (systolic blood pressure <100 mm Hg) are predictive of rebleeding. Coffee ground emesis has no prognostic value. A transfusion requirement of 4 units of blood or more per resuscitative event is predictive of rebleeding and death from UGI bleeding. Laboratory findings of note include thrombocytopenia, leukocytosis, and abnormal coagulation profile, all of which increase mortality. Corticosteroid use increases mortality, and anticoagulant use increases the risk of rebleeding.

Endoscopic

Only the finding of varices or gastric cancer has been shown clearly to be a predictor of death from UGI bleeding. Active arterial spurting has been associated inconsistently with increased mortality. Endoscopic findings, however, have clear prognostic value in accessing rebleeding rates. For reliable prognostication of rebleeding, endoscopy should be performed within 24 hours after presentation. Nearly 94% of episodes of rebleeding occur within 72 hours and 98% within 96 hours. The 3 endoscopic observations that are independent predictors of rebleeding regardless of the type of lesion are arterial spurting (rebleeding in 70%-90% of cases), visible vessel or pigmented protuberance (40%-50%), and adherent clot resistant to washing (10%-35%). Ulcers larger than 2 cm and posterior duodenal bulb ulcers also are predictive of rebleeding.

Predictive Models

Multiple models are available for predicting survival and the need for endoscopic intervention. Of note, these models cannot unequivocally predict the need for intervention. However, a patient has a very small chance (<1%) of requiring intervention if the Blatchford score is 0 (serum urea nitrogen <18.2 mg/dL, hemoglobin ≥13.0 g/dL for men and ≥12.0 g/dL for women, systolic blood pressure ≥110 mm Hg, pulse <100 beats per minute, and an absence of melena, syncope, cardiac failure, and liver disease).

Specific Lesions

Peptic Ulcers

The approach to a patient who has bled from peptic ulcer disease is determined at endoscopy. There are many options for endoscopic therapy. Thermal-coaptive coagulation involves the placement of the coagulating probe directly on the bleeding vessel. This is uniformly effective for vessels up to 2 mm in diameter with the heater probe (typical setting in cases of peptic ulcer disease, 30 J) or the BICAP probe (14-16 W). Injection therapy results in short-term tamponade and vasospasm and can be induced with the liberal use of epinephrine (1:10,000). Vasodestruction is long-term and can be induced by sclerosants or alcohol (total injection volume not to exceed 2 mL). Endoscopic clipping has not been shown to be any more effective than thermal therapy. However, it may have appeal for use in patients with coagulation disorders or in cases in which further coaptive coagulation may not be desirable.

Endoscopic therapy is indicated for patients with active arterial bleeding and those with a nonbleeding visible vessel (pigmented protuberance). An adherent clot is a predictor of rebleeding and can be managed with endoscopic therapy or high-dose proton pump inhibitor therapy (or both). All 3 endoscopic treatment options have been shown to have a relatively similar efficacy. However, epinephrine injection followed by a more permanent form of treatment (coagulation, vasodestruction, or clipping) has been shown to be more effective than epinephrine therapy alone. Patients with a clean ulcer base (rebleeding rates <5%) and a flat pigmented spot (rebleeding rates, 5%-10%) do not require endoscopic therapy and likely could be discharged soon after endoscopy. Deep ulcers may tend to expose larger vessels that may not be amenable to endoscopic coagulation. Deep ulcers in the stomach, particularly those in the upper body on the lesser curvature (left gastric artery), or posterior duodenal bulb (gastroduodenal artery) with nonbleeding visible vessels more than 2 to 3 mm in diameter should not be treated. Rebleeding after endoscopic therapy occurs 20% to 30% of the time. Re-treatment for recurrent bleeding achieves long-term hemostasis in more than 70% of cases.

If endoscopic therapy fails, angiographic embolization of the bleeding vessel is preferable to surgical intervention. No data support the use of histamine$_2$ (H_2)-blockers or antacids in controlling peptic ulcer bleeding. Several studies have suggested that high-dose proton pump inhibitor therapy is beneficial for patients with peptic ulcer bleeding and high-risk stigmata, both with and without endoscopic therapy. Presumably, the benefit is related to clot stabilization occurring in a nonacid environment. In vitro studies suggest that pH greater than 6.0 is required for platelet aggregation and fibrin formation, whereas pH less than 5.0 is associated with clot lysis. This level of pH increase is achieved best with proton pump inhibitor therapy administered as a continuous intravenous infusion. Octreotide may be of some benefit in torrential bleeding as a temporizing measure because of its effects on decreasing splanchnic blood flow.

Patients with UGI bleeding and *Helicobacter pylori* infection should be treated, and eradication of the *H pylori* infection should be proven. Patients taking NSAIDs should avoid them, if possible. Patients without a reversible cause of peptic ulcer disease should receive long-term ulcer prophylaxis with either a full-dose H_2-blocker (ranitidine 300 mg daily) or a proton pump inhibitor. Without treatment, recurrent ulcer bleeding will occur in approximately one-third of these patients within 3 to 5 years. This rate can be decreased to less than 10% with full-dose H_2-blocker prophylaxis. Ulcer rebleeding is uncommon in patients with proven eradication of *H pylori* infection who avoid the use of NSAIDs. However, ulcer prophylaxis may be reasonable for patients in whom *H pylori* infection has been eradicated but who have a clinically important comorbid condition, especially if they take NSAIDs continuously or intermittently.

Mucosal Erosive Disease

Endoscopic esophagitis, gastritis, and duodenitis are defined by the endoscopic findings of hemorrhage, erythema, or erosions. These lesions rarely are associated with major UGI bleeding. Large hiatal hernias can be associated with chronic blood loss related to Cameron lesions, which are linear erosions along the crests of gastric folds at or near the diaphragmatic hiatus. Gastric erosive disease usually is related to NSAID use, alcohol intake, or stress gastritis. Bleeding generally is minor unless ulceration develops. Prophylaxis of NSAID injury with misoprostol or omeprazole or treatment with cyclooxygenase-2–specific NSAIDs decreases the risk of ulcer development. Stress gastritis

leads to clinically significant UGI bleeding in more than 3% of patients in intensive care units. At higher risk are patients receiving mechanical ventilation for more than 48 hours, patients with coagulopathy, and patients with head injury or extensive burn injuries. Prophylactic therapy should be reserved for these groups. Maintenance of gastric pH greater than 4 with enteral feedings and use of H_2-receptor antagonists or proton pump inhibitors are effective for preventing stress ulcer bleeding. Proton pump inhibitor therapy appears more effective than H_2-blocker therapy for preventing bleeding. Sucralfate has been shown to be effective for prophylaxis of stress ulcer bleeding without affecting gastric pH; in some studies, it has been associated with less pneumonia and possibly less mortality than H_2 blockers.

Mallory-Weiss Tear

Mallory-Weiss tears occur at the gastroesophageal junction and often are present with a classic history of recurrent retching, frequently in an alcoholic patient, before the development of hematemesis. Most tears occur on the gastric side of the gastroesophageal junction, but 10% to 20% of them may involve the esophagus. Bleeding stops spontaneously in 80% to 90% of patients and rebleeding occurs in 2% to 5%. Endoscopic therapy with thermal coagulation or injection therapy is of benefit for active bleeding. Angiographic therapy with intra-arterial vasopressin or embolization also can be effective, as can oversewing the lesion intraoperatively.

Portal Hypertensive Gastropathy

Portal hypertensive gastropathy is more frequent in the proximal stomach than the distal stomach and gives the gastric mucosa a mosaic or snakeskin appearance, with or without red spots. Severe portal hypertensive gastropathy has the mosaic pattern as well as diffuse red spots and can be associated with both chronic and acute gastrointestinal tract bleeding. Bleeding usually is not massive, and therapy is directed at lowering portal pressure. Rebleeding can be decreased with nonselective β-blocker therapy.

Aortoenteric Fistula

Fistulas can occur between any major vascular structure and the gastrointestinal tract. Aortoesophageal fistulas are caused by thoracic aortic aneurysms, esophageal foreign bodies, or neoplasms. Up to 75% of aortoenteric fistulas communicate with the duodenum, usually in the distal third. These may develop from an aortic aneurysm but are related more commonly to abdominal aortic (graft) reconstructive surgery. Infection appears to have a major pathogenic role in the development of these fistulae, which usually develop off the origin of the graft, often with pseudoaneurysm formation. The classic "herald bleed," in which bleeding stops spontaneously hours to months before massive bleeding, occurs in about one-half of patients. Evaluation should begin with extended upper endoscopy to examine for evidence of distal duodenal bleeding (positive in <40% of cases) and to exclude other sources of bleeding. Explorative surgery is indicated for a patient with an aortic graft, severe bleeding, and negative endoscopic findings. Angiography rarely is helpful and may delay appropriate treatment. Computed tomography or magnetic resonance imaging may be helpful in demonstrating air surrounding the graft in proximity to the duodenum or an absence of a tissue plane between the graft and the duodenum, which suggests the diagnosis. The correct diagnosis is established preoperatively in as few as one-third of patients.

Hematobilia and Hemosuccus Pancreaticus

Hematobilia is manifested classically as UGI bleeding accompanied by biliary colic and jaundice. The diagnosis is made endoscopically by seeing blood coming from the ampulla. The most common cause of hematobilia is trauma, including liver biopsy, to the liver or biliary tree. Extrahepatic or intrahepatic artery aneurysms often are caused by trauma and may communicate with the bile ducts. Bleeding can be caused also by gallstones, hepatic or bile duct tumors, and cholecystitis.

In hemosuccus pancreaticus, the bleeding is usually from peripancreatic blood vessels into the pancreatic duct. This commonly is due to rupture of true aneurysms or pseudoaneurysms often associated with pancreatitis and pseudocysts. Angiography is used to locate the bleeding site. Transcatheter embolization is the treatment of choice. Surgery may be required for embolization failures.

Neoplasms

Bleeding can occur from primary UGI tumors (adenocarcinoma, stromal tumors, lymphomas, or neuroendocrine tumors) and, occasionally, metastatic UGI tumors (melanoma or breast). Gastrointestinal stromal tumors often appear as a submucosal mass with central ulceration and are not an infrequent cause of severe UGI bleeding. Effective therapy generally is surgical.

Vascular Anomalies

Anomalies With Skin Lesions. Vascular lesions can be seen throughout the gastrointestinal tract in several systemic diseases and syndromes such as Osler-Weber-Rendu disease (ie, hereditary hemorrhagic telangiectasia), the elastic tissue disorders of pseudoxanthoma elasticum and Ehlers-Danlos syndrome, CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome, and blue rubber bleb nevus syndrome. Endoscopic coagulation therapy is the treatment of choice. Therapy with high-dose estrogen-progesterone therapy is of debatable value but has been reported to decrease bleeding in patients with hereditary hemorrhagic telangiectasias not amenable to complete endoscopic therapy.

Anomalies Without Skin Lesions. Vascular ectasias can occur anywhere in the UGI tract but are more common in the duodenum and stomach, particularly in older patients and those with chronic renal failure or previous radiotherapy. These lesions are cherry red and often fernlike in appearance. Histologically, dilated, ectatic, or tortuous submucosal blood vessels (or a combination of these) are seen; the pathogenesis of these vessels is not known. These lesions may be diffuse or localized. Vascular ectasias are treated with endoscopic thermal coagulation. Estrogen-progesterone therapy has been shown to be effective occasionally and can be attempted when endoscopic therapy fails.

Gastric antral vascular ectasia, or "watermelon stomach," is a specific type of localized ectasia often seen in elderly women who present with iron deficiency anemia and evidence of mild UGI tract blood loss. This lesion is associated with several other disease processes, most notably, connective tissue disorders, atrophic gastritis, pernicious anemia, and portal hypertension. Red streaks that traverse the gastric antrum and converge at the pylorus, resembling the stripes on a watermelon, are seen with endoscopy. Histologically, large blood vessels with intravascular fibrin thrombi and fibromuscular hyperplasia are seen, but the diagnosis usually is made on the basis of the classic endoscopic appearance.

If iron replacement is inadequate to maintain a normal level of hemoglobin, endoscopic thermal therapy often is helpful. Argon plasma coagulation is the preferred thermal treatment for gastric antral vascular ectasia because of the large area usually requiring treatment. Occasionally, antrectomy is necessary.

A Dieulafoy lesion is an abnormally large submucosal artery that can rupture and bleed. The bleeding is arterial and is usually moderate to severe. Most of these lesions are within 6 cm of the esophageal junction, but they can occur in the duodenum and jejunum as well as in the esophagus, colon, rectum, and biliary tree. They can be difficult to diagnose when the bleeding has stopped, and endoscopy may need to be repeated several times to identify the lesion. When the lesion is identified, endoscopic tattooing of the lesion often is helpful, especially if surgical therapy is planned. A Dieulafoy lesion appears as a small protruding vessel surrounded by normal mucosa or as a minute mucosal defect. These lesions are amenable to conventional endoscopic therapy, band ligation, and endoscopic clipping. Rebleeding rates after endoscopic therapy are low. A nonbleeding visible vessel should be treated. Angiographic embolization can be effective in high-risk surgical patients.

Non-UGI Bleeding

Introduction

Gastrointestinal tract bleeding has been classified according to the level of the tract: 1) *upper*—proximal to the ampulla of Vater, 2) *mid*—from the ampulla of Vater to the terminal ileum, and 3) *lower*—distal to the terminal ileum. Only 3% to 5% of episodes of gastrointestinal tract bleeding originate from a mid-bowel source.

Depending on the transit time, which in turn is determined by the volume of bleeding, patients with non-UGI bleeding may present with melena, hematochezia, or occult bleeding. It is important to note that bacterial metabolism needs sufficient time for melena to be generated from fresh blood.

Hematochezia most commonly indicates bleeding from a colonic source. However, the source is more proximal in 5% to 10% of patients. It would be extremely uncommon for hematochezia to originate from a source in the proximal gastrointestinal tract without hemodynamic evidence of bleeding or clinical evidence of rapid gastrointestinal transit (eg, hyperperistalsis).

If blood is limited to the toilet paper or the surface of formed stool, a perianal source (eg, hemorrhoids or fissures) is likely. Tenesmus suggests a rectal origin (eg, proctitis). For all patients, the possibility of neoplasia must at least be considered and often excluded.

Specific Lesions

Diverticular Bleeding

Patients with diverticular bleeding typically present with acute blood loss, as manifested by maroon stools or hematochezia. Minor or occult bleeding is not characteristic of diverticular bleeding or diverticulosis. Diverticular bleeding and diverticulitis are distinct conditions that rarely occur together. Diverticular bleeding is painless except for the cramping that may occur with the cathartic effect of blood within the colon.

Diverticular bleeding is thought to originate more commonly from the right colon, where ostia tend to be wider and the colon wall thinner. Diverticular bleeding develops in an estimated 3% to 5% of patients with diverticulosis. Bleeding most commonly occurs during the sixth and seventh decades of life and stops spontaneously in more than 75% of patients. Generally, rebleeding occurs in about 15% to 20% of patients. After a second episode, the risk of rebleeding is approximately 25% to 50%.

For ongoing or recurrent bleeding, angiography often is performed with the intention of identifying an actively bleeding vessel. If the vessel is identified, transcatheter embolization can be attempted, although in some series colonic infarction has been as high as 20%. Transcatheter vasopressin can control bleeding in 90% of cases, but rebleeding rates are high. Endoscopic therapy has been reported to be safe and effective, but locating the actual bleeding lesion may be difficult.

Vascular Ectasia

Vascular ectasias are typically smaller than 5 mm and are found in 3% to 6% of patients undergoing colonoscopy. Most commonly, they are in the right colon but may occur anywhere in the gastrointestinal tract. These lesions are usually angiodysplasias, which are often multiple and believed to be related to the aging process. Less than 10% of patients with angiodysplasia eventually have bleeding. Not uncommonly, these lesions are uncovered by a bleeding diathesis, such as anticoagulation or platelet dysfunction. The lesions may lead to acute overt as well as occult gastrointestinal tract bleeding.

For many patients, iron repletion therapy alone is sufficient. Endoscopic therapy is effective but is associated with a significant rebleeding rate. Angiographic embolization can be used to control acute bleeding. Estrogen and progesterone when taken together may be of benefit for some patients, particularly those with hereditary hemorrhagic telangiectasia, but the data are conflicting. Octreotide and thalidomide have been shown to be of benefit in small trials of patients with obscure gastrointestinal tract bleeding presumed to be related to vascular ectasias.

Neoplasm

Patients with neoplasm of the colon and small bowel may present with either acute or occult non-UGI bleeding. Tumors of the small intestine may be a relatively common cause of obscure non-UGI bleeding in patients younger than 50 years and are malignant two-thirds of the time. Carcinoids, adenocarcinomas, and gastrointestinal stromal tumors account for most of these lesions.

Ischemic Colitis

Patients with ischemic colitis often present with pain and low-volume hematochezia. This may be seen in patients who have had abdominal vascular surgery, in those who have vasculitis or clotting disorders, or in those who receive estrogen therapy. However, in most cases, no etiologic factor is identified. Large-vessel disease is rarely found, and angiography generally is not indicated. There is no specific therapy, and recovery is usually complete in several days. Occasionally, however, a colonic stricture may develop.

Meckel Diverticulum

A Meckel diverticulum, a remnant of the vitelline duct, usually occurs 100 cm proximal to the ileocecal valve. Autopsy series suggest a prevalence rate of 0.3% to 3%. Approximately 50% of these diverticula contain gastric mucosa, and patients, typically a child or young adult, may present with bleeding.

Inflammatory Bowel Disease

Patients with inflammatory bowel disease may present with gross, bloody diarrhea, which is the classic presentation for ulcerative colitis. Major hemorrhage is uncommon but can occur.

Benign Rectoanal Disease

Patients with benign rectoanal disease often present with hematochezia. Painless hematochezia with blood on the toilet paper or the surface of formed stool is most suggestive of hemorrhoidal bleeding. Painful outlet bleeding is typical of a rectal fissure.

Stercoral ulcers are associated with constipation and occur most commonly in the rectosigmoid area or, occasionally, in the more proximal colon. They often become manifest after disimpaction. Solitary rectal ulcer syndrome often is associated with excessive straining. The ulcer usually occurs on the anterior wall, 6 to 10 cm above the anal verge. Both of these lesions may come to attention because of significant bleeding.

Patients with radiation proctitis may present months to years after receiving radiotherapy to the prostate or pelvic organs. Sigmoidoscopy shows characteristic mucosal telangiectasias. The bleeding is rarely severe, and endoscopic argon plasma coagulation therapy is the treatment of choice.

Infection

Infections may be associated with non-UGI bleeding. Obvious clues include a travel history or evidence of systemic toxicity such as fevers, rashes, arthralgias, eosinophilia, or diarrhea. In patients infected with human immunodeficiency virus, common causes of non-UGI bleeding are cytomegalovirus colitis and lymphoma.

NSAID Enteropathy and Colonopathy

Increasingly, NSAID enteropathy and colonopathy are being recognized as explanations for non-UGI bleeding. Autopsy studies have documented small intestinal ulcers in 8% of patients who had taken NSAIDs within the preceding 6 months. Diaphragmatic strictures are strongly suggestive of NSAID-induced inflammation. NSAIDs also are known to reactivate inflammatory bowel disease.

Approach

The evaluation and management of patients who present with non-UGI bleeding is determined largely by the clinical presentation and the differential diagnosis that has been generated. The following points are essential to keep in mind:

- Patients who are being evaluated because of positive findings on fecal occult blood testing require colonic imaging. Without signs or symptoms of UGI tract disease or iron deficiency, the value of esophagogastroduodenoscopy is debatable.
- Generally, the yield of a small-bowel follow-through study in patients with obscure gastrointestinal tract bleeding is less than 5%. This yield increases to 5% to 10% with enteroclysis.
- Technetium Tc 99m-tagged red blood cell radionuclide scans can detect bleeding rates as low as 0.1 mL/min. The patient may be scanned repeatedly over a 12- to 24-hour period in an attempt to capture intermittent bleeding. Radionuclide scans generally are not useful in identifying a specific site of bleeding. They are more sensitive for bleeding and are less invasive than angiography and often are used to determine the best timing for angiography.
- Mesenteric angiography is more accurate than radionuclide scans but requires a faster bleeding rate (>0.5 mL/min). Angiographic yields are much greater with active gastrointestinal tract bleeding (60%-70%) than when angiography is performed after bleeding has ceased (<20%). Angiographic therapy with transcatheter infusion of vasopressin or embolization has been effective but does carry a significant risk of bowel infarction.
- Capsule endoscopy clearly is the best method for evaluating the entire small bowel in patients with obscure bleeding. It shows an abnormal finding about 70% of the time. The technology for localization and blood detection is improving, but capsule retention that requires surgery is still an issue.
- Push enteroscopy has been reported to identify probable bleeding sites in 50% of patients with obscure gastrointestinal tract bleeding. This can be done with an adult or pediatric colonoscope, but the depth of insertion is greater with a dedicated enteroscope (length, 200-250 cm) used with an overtube. Of note, about 25% of the diagnoses made with push enteroscopy are within the reach of a standard endoscope.
- Balloon-assisted endoscopy can be performed by the peroral or perianal route (or both), with a diagnostic yield of greater than 60%. Endoscopic therapy can be administered. Double-balloon endoscopy appears to provide deeper small-bowel intubation than single-balloon or spiral endoscopy. Complete enteroscopy can be achieved with double-balloon endoscopy in over 40% of patients with the combined antegrade and retrograde approach.
- Intraoperative enteroscopy has been reported to detect abnormalities in about 70% of patients. However, recurrent bleeding is not uncommon, and only about 40% to 50% of these patients are free of bleeding at 2 years.
- Multiphasic computed tomographic enterography and magnetic resonance enterography are having an increased role in the evaluation of small-bowel blood loss. They appear particularly useful in the evaluation of bleeding related to small-bowel mass lesions.

Suggested Reading

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12

Vascular Disorders of the Gastrointestinal Tract[a]

STEPHEN C. HAUSER, MD

Mesenteric ischemia can occur from any of the myriad of conditions that decrease intestinal blood flow. Cappell divided these conditions into 1) secondary mesenteric ischemia due to extrinsic vascular compression or trauma (Box 12.1) and 2) primary mesenteric ischemia (mesenteric ischemic vasculopathy) resulting from arterial emboli, arterial or venous thrombi, low-flow states, or vasculitis. The esophagus receives its principal blood supply segmentally from small vessels from the aorta, right intercostal artery, bronchial arteries, inferior thyroid artery, left gastric artery, short gastric artery, and left phrenic artery. Vascular disease of the esophagus is extremely rare, except after surgical resection and in rare cases of vasculitis (Behçet syndrome). The stomach, duodenum, and rectum have numerous arterial inputs with rich collateralization. Vascular disorders that affect the stomach, duodenum, or rectum are also extremely rare, except for the reasons mentioned above for the esophagus.

The principal arterial supply to the gut distal to the esophagus is from the celiac, superior mesenteric, and inferior mesenteric arteries. Embolic disease most frequently affects the superior mesenteric artery because of its large diameter and narrow angle of takeoff from the abdominal aorta. Collaterals may include the meandering mesenteric artery or arc of Riolan at the base of the mesentery (connects the superior mesenteric and inferior mesenteric arteries), the marginal artery of Drummond along the mesenteric border (connects the superior mesenteric and inferior mesenteric arteries), the pancreaticoduodenal arcade (connects the celiac and superior mesenteric arteries), the arc of Barkow (connects the celiac and superior mesenteric arteries), and the arc of Buhler (connects the celiac and superior mesenteric arteries). They enlarge rapidly in response to localized mesenteric ischemia. The inferior mesenteric vein joins the splenic vein, which in turn joins the superior mesenteric vein to form the portal vein.

Patient History and Examination

Primary mesenteric ischemia is responsible for about 1 in 1,000 hospital admissions, with cases distributed equally between the small bowel and the large bowel. Risks include age (older than 50 years) and conditions that predispose to stasis, thrombosis, inflammation, or embolism of the mesenteric vasculature (Box 12.2). Symptoms may be acute (sudden, within hours), subacute (days), chronic (intermittent, over weeks to months), or a combination (usually acute and chronic).

Patients with acute mesenteric ischemia involving the small bowel often present with abdominal pain that is severe, persistent (lasting hours), and poorly localized. The pain typically is out of proportion to the findings on abdominal palpation (ie, pain is much greater than tenderness). Prompt evaluation is critical. Without early diagnosis and therapy, the mortality rate can be as high as 70%. Other nonspecific complaints can include fever, nausea, vomiting, abdominal distention, and diarrhea. Physical findings can include tachycardia, abdominal distention, diminished or increased bowel sounds, and nonspecific diffuse abdominal tenderness. Localized abdominal tenderness, rebound, rigidity, hypotension, altered mental status, and visible gastrointestinal tract bleeding usually are late manifestations of more severe ischemic damage to the small bowel. Occult gastrointestinal tract bleeding can be an early finding. Leukocytosis with

[a] Portions previously published in Hauser SC. Vascular diseases of the gastrointestinal tract. In: Goldman L, Ausiello D. Cecil textbook of medicine: neurology and general medicine. 23rd ed. Philadelphia (PA): Saunders Elsevier; c2008. p. 1061-70. Used with permission.

Abbreviations: CT, computed tomography; MDCTA, multidetector computed tomographic angiography

Box 12.1. Conditions Predisposing to Secondary Mesenteric Ischemia

- Adhesions
- Herniation
- Volvulus
- Intussusception
- Mesenteric fibrosis
- Retroperitoneal fibrosis
- Carcinoid syndrome
- Amyloidosis
- Malignancy (peritoneal, mesenteric, colonic)
- Neurofibromatosis
- Trauma

left shift, hemoconcentration, metabolic acidosis, bacteremia, and an increase in amylase, aspartate aminotransferase, lactate, creatine kinase, lactate dehydrogenase, or phosphate levels may or may not occur. These tests lack both sensitivity and specificity, but when results are abnormal, they suggest more advanced (necrotic) bowel ischemia. Attention to predisposing conditions,

Box 12.2. Conditions Predisposing to Primary Mesenteric Ischemia

- Atherosclerosis or fibromuscular dysplasia
- Cholesterol atheromatous embolism
- Hypercoagulable or hyperviscosity states
- Vasculitis (Behçet syndrome, Buerger disease, Churg-Strauss syndrome, Cogan syndrome, Crohn disease, cryoglobulinemia, dermatomyositis, Fabry disease, giant cell arteritis, Henoch-Schönlein purpura, hypersensitivity vasculitis, Kawasaki disease, Köhlmeier-Degos syndrome, lymphocytic phlebitis, mesenteric phlebosclerosis, polyarteritis nodosa, rheumatoid arthritis, syphilis, systemic lupus erythematosus, Takayasu arteritis, thromboangiitis obliterans, granulomatosis with polyangiitis [formerly Wegener granulomatosis])
- Cardiac arrhythmias, valvular disease, subacute bacterial endocarditis, myxoma
- Cardiomegaly, myocardial dyskinesia, intracardiac thrombosis
- Cardiac catheterization, myocardial infarction, congestive heart failure
- Aortic or mesenteric artery aneurysm or dissection
- Low-flow states, systemic hypotension
- Vasoconstrictive agents (amphetamines, cocaine, digitalis, ergot, pseudoephedrine, sumatriptan, vasopressin)
- Abdominal trauma
- Radiation

their extraintestinal manifestations (congestive heart failure, hypotension, sepsis, arrhythmias, or splanchnic vasoconstrictors such as digoxin and cocaine), and their initial management are critical in resuscitation of the patient (replacing volume, enhancing cardiac output, diminishing splanchnic vasoconstriction, and administering broad-spectrum antibiotics).

Patients with primary mesenteric ischemia of the colon (ischemic colitis) usually present with acute abdominal pain (commonly left lower quadrant pain), often with urgency, diarrhea, and passage of bright red blood per rectum. Overall, colonic ischemia has a much better outcome than does small-bowel ischemia.

Initial Diagnostic Evaluation

For an acutely ill patient, plain abdominal radiographs are important to rule out secondary causes of mesenteric ischemia and other causes of acute abdominal pain, principally obstruction and perforation. "Thumbprinting" due to submucosal edema may be seen, as well as an ileus pattern. Pneumatosis intestinalis and portal venous gas are late findings that suggest transmural necrosis of the intestine (gangrene).

Contrast-enhanced abdominal-pelvic computed tomography (CT) may help exclude other causes of acute intra-abdominal pain and has been recommended to diagnose acute (or acute-on-chronic) mesenteric venous thrombosis in patients with a history of deep vein thrombosis or thrombophlebitis or a family history of a hypercoagulable state. CT findings may be normal in acute mesenteric ischemia involving the small bowel or may show nonspecific changes such as bowel wall thickening, submucosal hemorrhage, mesenteric stranding, portal venous gas, and pneumatosis. Multidetector CT angiography (MDCTA) has been shown to have a greater sensitivity and specificity (each up to 95%) than standard CT (each approximately 65%). Magnetic resonance angiography is less sensitive for more peripheral emboli and is often less readily available. CT should not defer resuscitation or arteriography in very ill patients with suspected acute mesenteric ischemia of the small bowel. Patients with subacute or chronic pain syndromes benefit from a more complete evaluation, including CT and duplex ultrasonography (see below).

Acutely ill patients with suspected small-bowel ischemia require prompt diagnosis and treatment, for which selective mesenteric arteriography is the standard. In many instances, the diagnostic information obtained by the performance of MDCTA is sufficient, obviating the need for angiography. If angiography is not readily available or transmural intestinal necrosis (gangrene) is suspected, laparotomy is indicated. Resuscitation and administration of broad-spectrum antibiotics constitute initial therapy for all patients.

Superior Mesenteric Artery Embolus

Superior mesenteric artery emboli are common, accounting for 5% of cases of peripheral emboli and 50% of cases of primary mesenteric ischemia of the small bowel. The emboli are usually from the heart; an aortic origin (atheromatous cholesterol embolism) is less common. Emboli usually obstruct distally to the origin of the superior mesenteric artery, near the origin of the middle colic artery, sparing the proximal jejunum and the right colon. Arrhythmias, cardioversion, cardiac catheterization, myocardial infarction or dyskinesia, congestive heart failure, valvular heart disease, atheromatous cholesterol embolism, previous embolism, and age older than 50 years are major risk factors. MDCTA is very reliable for the diagnosis of superior mesenteric artery embolism

(mesenteric fat stranding, mesenteric and peritoneal fluid, bowel wall thickening, bowel dilatation, abnormal bowel wall enhancement after intravenous contrast administration, and emboli).

Peritonitis requires laparotomy, with or without resection and with or without embolectomy. Otherwise, embolectomy (usually surgical) is indicated. Patients with acute onset of a partial or small occlusion of a distal branch of the superior mesenteric artery may be candidates for thrombolytic therapy, intra-arterial papaverine, and anticoagulation (Figure 12.1). Generalized vasoconstriction of the superior mesenteric artery occurs from occlusion of a single branch of the artery and often persists after embolectomy. Hence, many experts recommend intra-arterial papaverine before and for 24 hours after embolectomy or until a second-look operation (if indicated) is performed. Prophylaxis against further embolization (anticoagulation) usually is indicated preoperatively and then restarted 24 to 48 hours postoperatively.

Superior Mesenteric Artery Thrombus

Superior mesenteric artery thrombus accounts for about 15% of cases of primary mesenteric small-bowel ischemia. Risk factors for superior mesenteric artery thrombus include old age, low-flow states (arrhythmia, hypotension, sepsis, dialysis, vasoconstrictive drugs, myocardial infarction, dyskinesia, and congestive heart failure), atherosclerosis (acute-on-chronic ischemia, hypertension, diabetes mellitus, hyperlipidemia, smoking history, and vasculopathy), hypercoagulable states, vasculitis, fibromuscular dysplasia, trauma, and aortic or mesenteric artery aneurysm. Up to one-third of patients have a history of chronic mesenteric ischemia (see below). Thrombosis usually occurs at the origin of the superior mesenteric artery or within the first 2 cm, without sparing the proximal jejunum and the right colon. MDCTA is used to confirm the diagnosis. With magnetic resonance angiography, the degree of stenosis can be overestimated. Therapy usually involves intra-arterial papaverine and surgical thrombectomy or surgical bypass grafting, bowel resection, or a combination of these. In selected cases, intra-arterial angioplasty with or without stenting may be therapeutic.

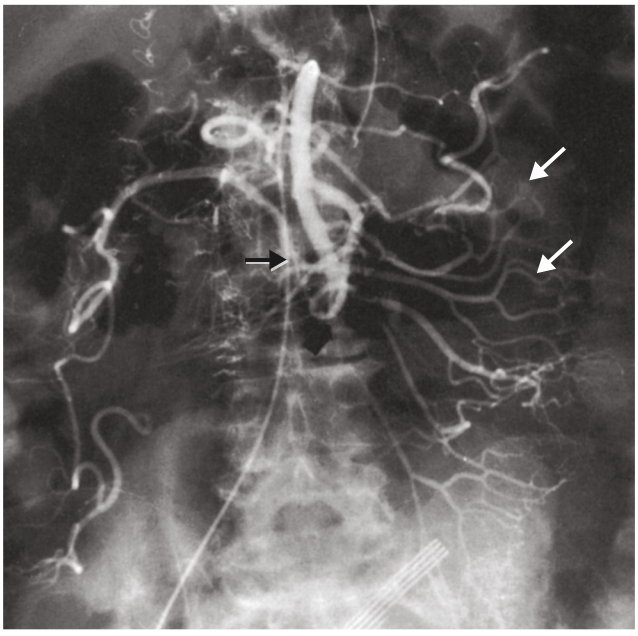

Figure 12.1. Embolic Occlusion of the Proximal Superior Mesenteric Artery. Anteroposterior view of the aorta shows the normal-appearing proximal jejunal arterial branches (white arrows) and the abrupt cutoff (black arrow) of the superior mesenteric artery. (Adapted from McKinsey JF, Gewertz BL. Acute mesenteric ischemia. Surg Clin North Am. 1997 Apr;77[2]:307-18. Used with permission.)

Nonocclusive Mesenteric Ischemia

Nonocclusive mesenteric ischemia accounts for 20% of cases of acute primary mesenteric ischemia of the small bowel. Risks for low-flow state include decreased cardiac output (myocardial infarction or dyskinesia, arrhythmia, shock, sepsis, pancreatitis, burns, multiple organ failure, congestive heart failure, or hemorrhage), vasospasm (digoxin, α-adrenergic agonists, amphetamines, or cocaine), dialysis, and pre-existing atherosclerotic disease (hypertension, diabetes mellitus, hyperlipidemia, or vasculopathy). Onset of symptoms may be subacute as well as acute. Compared with patients who have acute mesenteric ischemia due to arterial embolus or thrombus, patients with nonocclusive mesenteric ischemia less often have pain and more often present with nausea, abdominal distention, diarrhea, fever, or altered mental status. Angiography can be diagnostic (lack of thrombus or embolus, alternating spasm and dilatation ["string-of-sausages" sign], pruning, and spasm of mesenteric arcades) (Figure 12.2). MDCTA can show bowel wall changes and diffusely narrowed arteries. Treatment involves optimization of cardiac output, avoidance of vasospastic medications, and prolonged (up to several days) selective intra-arterial infusion of vasodilators such as papaverine, tolazoline, nitroglycerin, or glucagon. Laparotomy with or without resection and warm saline lavage may be needed in selected cases. Anticoagulation generally is not prescribed. Broad-spectrum antibiotics should be administered.

Mesenteric Venous Thrombosis

Mesenteric venous thrombosis, usually superior mesenteric vein thrombosis (up to 95% of cases), accounts for about 5% to 10% of cases of acute mesenteric ischemia. Risk factors include a personal or family history of hypercoagulopathy and a history of deep vein thrombosis. Causes include hypercoagulable states, hyperviscosity syndromes, intra-abdominal infections (pylephlebitis, diverticulitis, and appendicitis) or inflammation (Crohn disease and pancreatitis), malignant obstruction, portal hypertension, vasculitis, and trauma (Box 12.3). Symptoms may be acute (hours) or subacute-chronic (days to months) and include abdominal pain (either severe and out of proportion to physical findings or less severe and vague), anorexia, nausea, vomiting, diarrhea, constipation, abdominal distention, and gastrointestinal tract bleeding. Patients may present with bacteremia (especially from *Bacteroides*).

Because the differential diagnosis is broad and includes obstruction, perforation, and other causes of acute abdominal pain and acute mesenteric ischemia, the initial evaluation usually involves plain abdominal radiography and contrast-enhanced CT; the latter generally is diagnostic of mesenteric venous thrombosis with or without portal vein or splenic vein thrombosis (Figure 12.3). Although angiography is less reliable for the diagnosis of mesenteric venous thrombosis, it allows intra-arterial infusion of vasodilators.

Therapy involves laparotomy (with or without bowel resection when infarction is suspected), fluid resuscitation, broad-spectrum antibiotics, avoidance of vasoconstrictors, a nasogastric tube (if there is distention), and anticoagulation (in the absence of

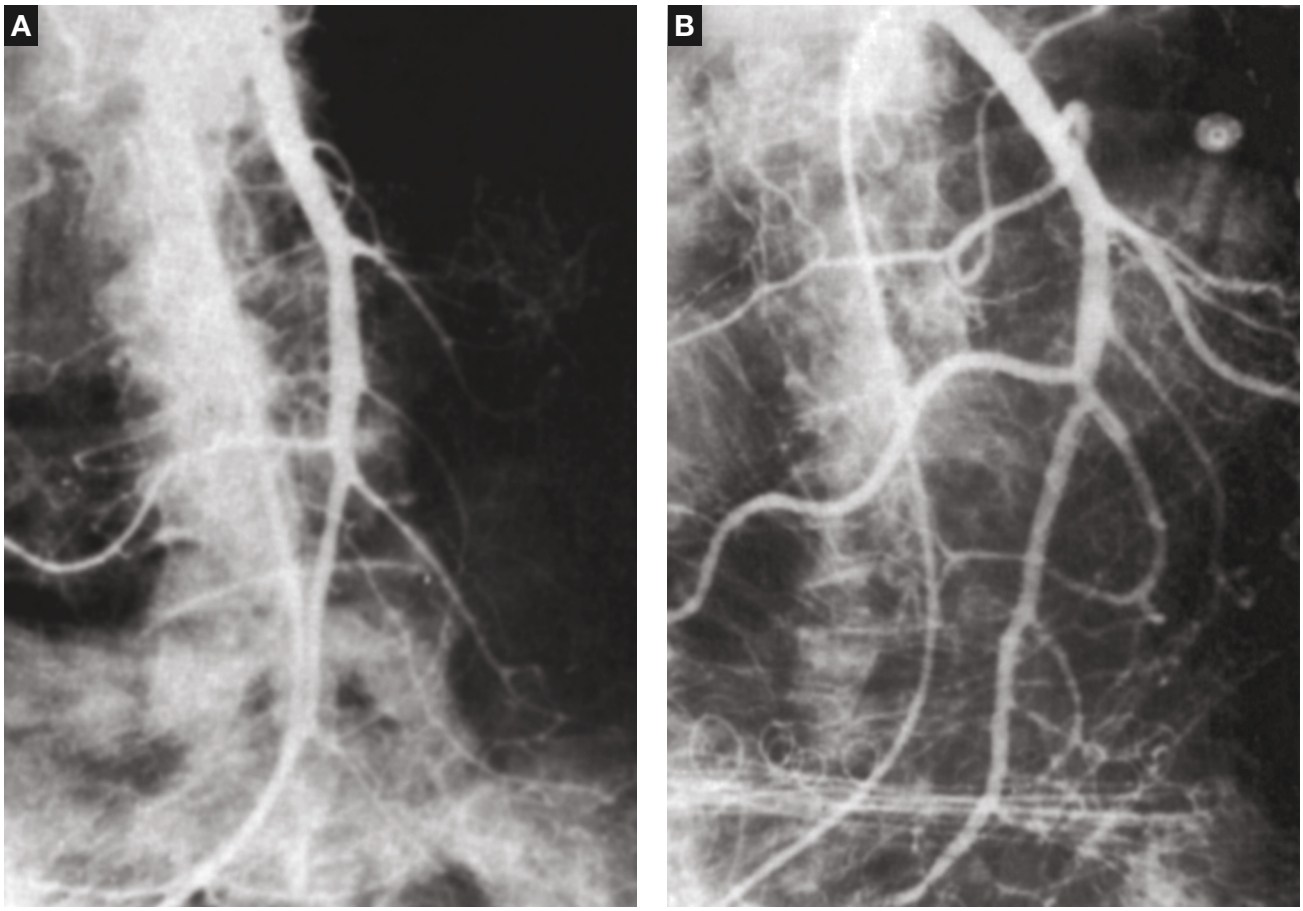

Figure 12.2. Nonocclusive Mesenteric Ischemia. A, Angiogram before treatment with papaverine shows spasm of main superior mesenteric artery, origins of its branches, and the intestinal arcades. B, Angiogram after 36 hours of papaverine infusion shows that the arteriospasm has resolved. The abdominal symptoms and signs also had resolved. (Adapted from Boley SJ, Brandt LJ, Veith FJ. Ischemic disorders of the intestines. Curr Probl Surg. 1978 Apr;15[4]:1-85. Used with permission.)

bleeding). Selected patients with acute onset of mesenteric venous thrombosis may be candidates for thrombolytic therapy, followed by anticoagulation. Underlying conditions such as hypercoagulable states, hyperviscosity syndromes, intra-abdominal infections, and malignancy require concomitant diagnosis and treatment.

Patients with mesenteric venous thrombosis may present with a subacute or chronic illness, with vague abdominal pain and distention, or with no symptoms. Mesenteric venous thrombosis may be an incidental CT finding (multiple collateral vessels) in patients with portal hypertension, chronic pancreatitis, or malignancy. Long-term anticoagulation should be considered except for higher-risk patients, such as the elderly or those with portal hypertension and prominent varices or portal hypertensive gastropathy.

Splenic vein thrombosis is usually due to pancreatitis, malignancy such as pancreatic cancer, or trauma. Isolated gastric varices and splenomegaly develop in many of the patients. For symptomatic patients (gastric variceal bleeding or hypersplenism), splenectomy is the best treatment.

Chronic Mesenteric Ischemia

Risk factors for chronic mesenteric ischemia include older age, atherosclerosis, vasculitis, and aortic aneurysm. A common history includes previous vascular disease, hypertension, diabetes mellitus, renal insufficiency, and smoking.

Patients with classic chronic mesenteric ischemia present with episodic ischemic, upper abdominal or midabdominal pain that typically occurs 15 to 30 minutes postprandially, lasts 1 to 3 hours, and becomes worse with time. Thus, patients lose weight because of fear of eating (sitophobia). Nausea, vomiting, bloating, diarrhea, and constipation also can occur. Some patients may have malabsorption, otherwise unexplained gastroduodenal ulcerations, and small-bowel biopsy findings of nonspecific surface cell flattening, chronic inflammation, and villous atrophy. More than one-half of patients have a bruit detected on abdominal examination.

With these patients, arteriography usually shows atherosclerotic stenosis of the origin of at least 2 of the 3 major visceral arteries. However, this is a common angiographic finding in otherwise healthy age-matched controls. Doppler ultrasonography—if the celiac and superior mesenteric arteries can be visualized (each is visualized in about 80% of cases)—may show increased flow velocities, consistent with marked stenosis. MDCTA and magnetic resonance imaging also may be useful in the identification of proximal large-vessel arterial lesions. However, it is crucial to consider the diagnosis, exclude other causes of abdominal pain and other symptoms (ie, pancreatic cancer, gastric cancer, gastroparesis, small intestinal bacterial overgrowth syndromes, partial small-bowel obstruction, biliary disease, gastric volvulus, or paraesophageal hernias), and obtain arteriographic results consistent with the clinical findings. Surgical reconstruction and, in selected cases, angioplasty with or without stents can be therapeutic.

Box 12.3. Causes of Mesenteric Venous Thrombosis

Hypercoagulable and hyperviscosity states
- Antiphospholipid syndrome
- Antithrombin deficiency
- C677T *MTHFR* gene mutation
- Estrogen or progesterone
- G1691 factor V gene mutation
- G20210A factor II gene mutation
- Hyperfibrinogenemia
- Primary myeloproliferative disorder
- Protein C deficiency
- Protein S deficiency
- Sickle cell disease
- Thrombocytosis

Intra-abdominal infections and inflammation
- Abscess
- Appendicitis
- Cholecystitis
- Crohn disease
- Diverticulitis
- Neonatal omphalitis
- Pancreatitis

Malignant obstruction

Portal hypertension
- Cirrhosis
- Sclerotherapy of varices

Trauma

Vasculitis

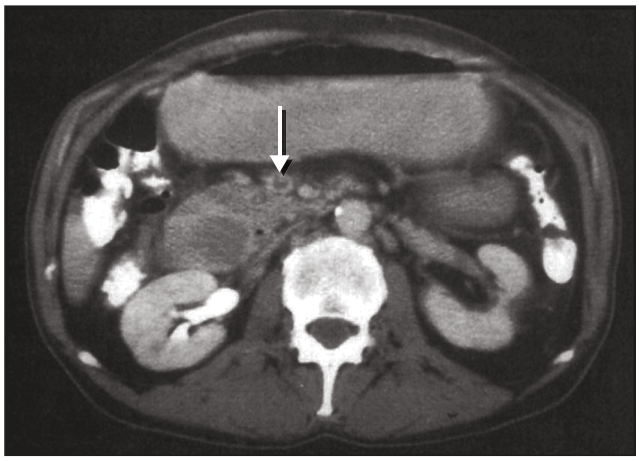

Figure 12.3. Acute Mesenteric Venous Thrombosis. Abdominal computed tomogram shows a thrombus (arrow) in the superior mesenteric vein. (Adapted from Rhee RY, Gloviczki P. Mesenteric venous thrombosis. Surg Clin North Am. 1997 Apr;77[2]:327-38. Used with permission.)

Ischemic Colitis

Ischemic colitis represents nearly one-half of all cases of mesenteric ischemia and accounts for nearly 1 in 2,000 hospital admissions. Most cases are acute and self-limited, occurring in persons older than 60 years and without an apparent cause. Transient nonocclusive hypoperfusion involving a segment of the colon may be the cause, and subtle hypercoagulable states may be contributory. Atherosclerotic or thrombotic occlusion of the inferior mesenteric artery or its branches and nonocclusive low-flow states are not uncommon causes of ischemic colitis (with associated vasospasm). Less common causes include embolus, vasculitis, hypercoagulable states, iatrogenic ligation of the inferior mesenteric artery (aortic surgery), and colonic obstruction (colon cancer, diverticulitis, or strictures). Other unusual associations include long-distance running (usually affecting the cecum), intra-abdominal infections or inflammatory disease, pit viper bite, scuba diving, and use of birth control pills, danazol, alosetron, tegaserod, various enemas, nonsteroidal antiinflammatory drugs, interferon with ribavirin, digitalis, vasopressin, gold, pseudoephedrine, psychotropic drugs, ergot, amphetamines, cocaine, or sumatriptan.

Gastrointestinal tract infections from several agents (cytomegalovirus, *Escherichia coli* O157:H7 and other Shiga toxin–producing bacteria, *Klebsiella oxytoca*, and *Clostridium difficile*) and chronic inflammatory bowel disease can mimic ischemic colitis clinically, endoscopically, and histologically. Ischemic colitis due to low-flow states often affects watershed areas such as the splenic flexure, the descending colon, the rectosigmoid junction, and the right colon. The splenic flexure is less often involved when the inferior mesenteric artery is acutely occluded (during aortic surgery) because of collaterals from the superior mesenteric artery. Often, but not always, the rectum is spared in ischemic colitis.

The clinical symptoms of ischemic colitis vary but often include acute abdominal pain (in two-thirds of patients, usually in the left lower quadrant), urgency, diarrhea, distention, anorexia, nausea, vomiting, or bright red blood or maroon material per rectum (variable amounts), or some combination of these. Physical findings often include 1 or more of the following: abdominal tenderness over the affected bowel, distention, fever, and tachycardia. Laboratory findings range from normal in patients with less severe ischemic colitis to those found in persons with severe ischemic necrosis (see above). Plain radiographs of the abdomen may show evidence of submucosal edema and hemorrhage ("thumbprinting"), or the findings may be nonspecific. Colonoscopy often provides endoscopic and histologic findings consistent with ischemic colitis (segmental, patchy ulceration, long linear ulceration [single-stripe sign], edema, erythema, and submucosal hemorrhagic or purple nodules) and helps exclude other causes of abdominal pain and gastrointestinal tract bleeding. CT may help exclude other disorders, especially in more symptomatic, sicker patients. Gastrointestinal tract infections (acute bacterial colitis, *C difficile* infection, and parasitic infections), inflammatory bowel disease, diverticulitis, pancreatitis, and other causes of acute abdominal pain (pelvic disorders in women) need to be excluded. Typically, angiography and MDCTA are not required but may be helpful for patients who have more severe ischemic colitis and should be performed if patients have right-sided involvement (which can imply involvement of the distal small bowel). Patients with right-sided ischemic colitis have more pain, less bleeding, and a worse outcome, especially those receiving hemodialysis.

As for all types of mesenteric ischemia, treatment depends on the cause and includes supportive treatment (volume replacement, correction of low-flow states, broad-spectrum antibiotics, transfusions, and avoidance of vasoconstrictive medications) and, in selected cases, surgery (signs and symptoms of transmural necrosis, perforation, massive bleeding, recurrent sepsis, failure

to improve over time, or stricture formation). In most patients, ischemic colitis resolves promptly with supportive therapy alone. Patients younger than 60 years or those with recurrent episodes should be evaluated for thrombophilic states. Studies also lend support to the usefulness of thrombophilic screening in older patients who have idiopathic ischemic colitis.

Miscellaneous Syndromes

Celiac Artery Compression

Celiac artery compression, also called *median arcuate ligament syndrome*, is a rare syndrome with abdominal pain, which is caused most likely by extrinsic compression of the celiac axis (neural structures and the wall of the celiac artery) by the arcuate ligament. Rarely, the superior mesenteric artery also may be involved. Ischemia to the gut is unlikely to cause the pain (because only 1 vessel is involved and collateral vessels are well developed). Celiac artery compression usually occurs in young women, often with upper abdominal pain (especially after eating, because of increased blood flow through the celiac artery), often with weight loss, and with a loud systolic bruit detected in the epigastric area on physical examination. Lateral aortography should demonstrate a typical concave defect over the superior aspect of the celiac artery near its takeoff from the aorta, with respiratory variability. Collaterals may be seen. Surgical release of the compression of the celiac artery or reconstruction of the artery (or both) may be curative. Preoperatively, other possible causes of the symptoms must be excluded.

Vasculitis and Visceral Aneurysms

Many vasculitic syndromes can involve the gastrointestinal tract. Buerger disease (thromboangiitis obliterans) can cause multiple distal occlusions of small and medium-sized arteries of the mesenteric circulation. Polyarteritis nodosa typically involves small and medium-sized arteries, resulting in segmental microaneurysms, and affects the small bowel more often than the colon. Many patients have fever, abdominal pain, an increased erythrocyte sedimentation rate, hypertension, and multiple organ involvement. Some have gastrointestinal tract bleeding or perforation. Nearly one-half of the patients are infected with hepatitis B virus. Also, the gallbladder, liver, pancreas, and spleen may be involved. The gastrointestinal tract often is involved in Churg-Strauss syndrome (small and medium-sized arteries) and Henoch-Schönlein purpura (sometimes with *E coli* O157:H7 or *Campylobacter jejuni* infection). With Henoch-Schönlein purpura, IgA is deposited in multiple organs, including the walls of small blood vessels. Abdominal pain, gastrointestinal tract bleeding, arthritis, and palpable purpura often are present. Patients with severe rheumatoid arthritis, high titers of rheumatoid factor, nodules, cryoglobulinemia, low serum levels of complement, and extra-articular manifestations also may have vascular lesions involving the gut, pancreas, gallbladder, spleen, and appendix, as may patients with systemic lupus erythematosus (especially those with antiphospholipid or cardiolipin antibodies).

Vasculitis with bowel involvement is less common in patients with giant cell arteritis (large and medium-sized arteries), Takayasu arteritis (large and medium-sized arteries), hypersensitivity vasculitis (small arterioles, capillaries, and venules), cryoglobulinemia (small blood vessels), Behçet syndrome (small and medium-sized arteries and veins), or granulomatosis with polyangiitis (formerly Wegener granulomatosis) (affecting small and medium-sized arteries). Mesenteric venous involvement can occur with Churg-Strauss syndrome, systemic lupus erythematosus, Behçet syndrome, lymphocytic phlebitis, and idiopathic mesenteric phlebosclerosis.

Bowel rupture as well as large-vessel rupture can be a life-threatening complication of the vascular type of Ehlers-Danlos syndrome, with thin fragile skin, easy bruisability, hyperextensible distal interphalangeal joints, and splanchnic artery aneurysms due to a defect in type III collagen. Similar vascular catastrophes with gastrointestinal tract bleeding can occur in patients with pseudoxanthoma elasticum type I, which often is accompanied by peau d'orange skin and choroiditis. Occasionally, mesenteric vasculitis is found in patients with carcinoid syndrome. Splanchnic artery aneurysms include splenic artery aneurysms (due to atherosclerosis, fibrodysplasia of the media, portal hypertension, pregnancy, pancreatitis, vasculitis, infection, or trauma), hepatic artery aneurysms (often due to trauma, including liver biopsy), mesenteric aneurysms (often due to atherosclerosis), and aneurysms of the arterial supply to the pancreas (often due to pancreatitis and pseudocysts)—patients with any of these may present with gastrointestinal tract or intraperitoneal hemorrhage. Hemobilia may occur with hepatic artery aneurysms. Symptomatic aneurysms, sizable aneurysms (≥1 cm for a hepatic artery aneurysm and ≥2 cm for a splenic artery aneurysm), and splenic artery aneurysms discovered during pregnancy should be treated, usually by interventional radiology.

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13

Gastrointestinal Manifestations of Systemic Disease[a]

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Many systemic diseases can have gastrointestinal (GI) manifestations. Both the gut and the liver may be the main targets of the disease process, or they may be affected indirectly; in either case, the GI symptoms or signs may be the initial reason for seeking medical attention. This chapter is an overview of the more common systemic disorders that have well-recognized GI and liver manifestations, with an emphasis on disorders not considered elsewhere in this book.

Cardiovascular Diseases

Aortic Stenosis

Aortic stenosis is associated with an increased incidence of GI bleeding (Heyde syndrome). The GI bleeding in patients with aortic stenosis is typically from small-intestinal angiectasias. In patients with aortic stenosis, the aortic wall shear stress is high. As a result of high macrovascular shear stress, there is increased consumption of high-molecular-weight multimers of von Willebrand factor (vWF) from the increased activity of shear-dependent vWF-cleaving metalloprotease. This leads to a relative deficiency of high-molecular-weight multimers of vWF and an acquired type IIA von Willebrand disease that predisposes the patient to clinically manifest bleeding from angiectatic lesions in the GI tract. Support for this pathophysiologic mechanism comes from observations that the severity of GI bleeding from GI angiectasias decreases after aortic valve replacement, which is associated with a concomitant increase in the level of circulating high-molecular-weight vWF multimers. Similarly, hypertrophic obstructive cardiomyopathy has been associated with GI angiectasias.

Heart Failure

Impairment of myocardial filling or contraction results in inadequate perfusion of tissues and a resultant inability to maintain metabolic demands. Heart failure leads to congestion of the mesenteric venous system, which can manifest with anorexia, nausea, bloating, and abdominal pain. In extreme cases, mesenteric venous congestion results in diarrhea, malabsorption, protein-losing enteropathy, and the clinical picture of cardiac cachexia. Hepatic congestion from right-sided heart failure may cause hepatomegaly, jaundice, abnormal liver test results, and a high serum-ascites albumin gradient. In cases of prolonged hepatic congestion from heart failure, cardiac cirrhosis may develop.

Vascular Diseases

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) (Osler-Weber-Rendu syndrome) is an autosomal dominant disorder with high

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Abbreviations: ALA, aminolevulinic acid; BD, Behçet disease; BRBNS, blue rubber bleb nevus syndrome; CF, cystic fibrosis; CVID, common variable immunodeficiency; DIOS, distal intestinal obstruction syndrome; DM, diabetes mellitus; EPS, encapsulating peritoneal sclerosis; GI, gastrointestinal; GVHD, graft-versus-host disease; HHT, hereditary hemorrhagic telangiectasia; HSP, Henoch-Schönlein purpura; KTW, Klippel-Trénaunay-Weber; PAN, polyarteritis nodosa; PCI, pneumatosis cystoides intestinalis; RA, rheumatoid arthritis; SCD, sickle cell disease; SIBO, small intestinal bacterial overgrowth; SLE, systemic lupus erythematosus; vWF, von Willebrand factor

penetrance and an estimated prevalence of 1 per 10,000. It is characterized by the development of telangiectasias and arteriovenous malformations throughout the body. Mucocutaneous telangiectasias typically develop in the second decade of life, leading to recurrent, spontaneous epistaxis, which is the most common manifestation of HHT.

Clinical criteria for the diagnosis of HHT are the following:

1. *Epistaxis*—spontaneous, recurrent nosebleeds, usually present since adolescence
2. *Telangiectasias*—multiple lesions at characteristic sites (lips, oral cavity, fingers, nose)
3. *Visceral involvement*—pulmonary, liver, central nervous system, GI tract
4. *Family history*—a first-degree relative with definite HHT

If 3 of the 4 criteria are present, the clinical diagnosis of HHT is definite. If 2 criteria are present, the diagnosis of HHT is probable. If only 1 criterion is present, HHT is unlikely.

GI hemorrhage occurs in 30% of HHT patients and does not usually start until the fourth or fifth decade of life. HHT is the most common cause of diffuse vascular malformations of the liver in adults. Although hepatic vascular malformations are present in the majority of patients with HHT, symptoms occur in only 30%. With the dual blood supply to the liver, 3 types of vascular shunts may develop, which give rise to 3 distinct clinical presentations: high-output heart failure, portal hypertension, and biliary disease (Box 13.1).

After recurrent epistaxis, GI bleeding is the most common clinical manifestation of HHT. Telangiectasias are readily visible on endoscopy, occurring throughout the GI tract. Endoscopic ablation with argon plasma coagulation is commonly used as treatment.

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus syndrome (BRBNS) is a rare disorder characterized by the development of venous malformations in many organs, with the skin and GI tract most commonly involved. It is usually sporadic, but it may be inherited in an autosomal dominant fashion. The 2 most common manifestations of BRBNS are skin lesions alone or iron deficiency anemia from GI bleeding. Most patients with GI bleeding from BRBNS are asymptomatic and generally respond to blood transfusion and oral iron supplementation. Capsule endoscopy is a noninvasive way to exclude or confirm GI involvement, but the distribution of lesions is only important to know if bleeding cannot be controlled by conservative measures. Caution should be used when attempting endoscopic ablation of lesions, which may involve the full thickness of the bowel wall, so that perforation does not occur. The venous malformations can cause numerous extraintestinal complications, including orthopedic deformities, central nervous system involvement, spinal cord compression, hemothorax, and hemopericardium.

Box 13.1. Three Distinct Clinical Manifestations of Liver Involvement in Hereditary Hemorrhagic Telangiectasia

1. *High-output heart failure* results from an arteriovenous shunt involving the hepatic artery and hepatic veins. This is the most common initial manifestation of liver involvement in hereditary hemorrhagic telangiectasia.
2. *Portal hypertension* results from a hepatic artery–portal vein fistula and occurs most commonly with ascites.
3. *Biliary disease* with bile duct abnormalities is similar to sclerosing cholangitis. Bile duct abnormalities result from ischemia of the biliary tree because the bile ducts obtain all their blood supply from the hepatic artery. Hepatic artery–hepatic vein or hepatic artery–portal vein fistulas may cause biliary ischemia. Clinical manifestations include right upper quadrant pain and cholestasis with or without cholangitis.

Klippel-Trénaunay-Weber Syndrome

Klippel-Trénaunay-Weber (KTW) syndrome is a rare congenital vascular anomaly characterized by the clinical triad of 1) soft tissue and bony hypertrophy of an extremity, 2) varicose veins limited to the affected side, and 3) vascular nevus of the hypertrophied extremity. The cause of this syndrome is unknown. KTW can be diagnosed by the presence of any 2 of these 3 clinical features, with 60% of KTW patients having the full triad. Visceral hemangiomas in KTW have been described involving organs such as the GI tract, liver, spleen, bladder, kidney, lung, and heart. GI hemorrhage is a potentially serious complication resulting from diffuse hemangiomatous involvement of the gut. Transfusion-dependent anemia and life-threatening bleeding may result from extensive cavernous hemangiomas involving the rectum. Although diffuse cavernous hemangiomas of the distal colon and rectum are the most commonly reported causes of GI bleeding in KTW, other potential causes of GI hemorrhage related to KTW include localized rectovaginal varices caused by an obstructed internal iliac system and portal hypertension–related bleeding from a hypoplastic portal venous system. GI bleeding in KTW may be enhanced by consumption coagulopathy (Kasabach-Merritt syndrome) resulting from intravascular clotting within the venous sinusoids of the visceral hemangiomas. Endoscopic therapy has a limited role in the management of colorectal intestinal hemangiomas in KTW and is best reserved for management of localized lesions or ablation of postoperative residual disease. Resection of the involved bowel segment is usually necessary to adequately control bleeding.

Degos Disease

Degos disease (malignant atrophic papulosis) is a vasculopathy of unknown cause characterized by a predominantly noninflammatory vascular occlusive process, mainly affecting arterioles. Progressive arteriolar occlusion results in tissue ischemia and infarction, which are responsible for the clinical manifestations of the disease. Age, at onset of the disease, ranges from the first months of life to the seventh decade. In the GI tract, the submucosal arteries are typically affected, causing infarction of the bowel. Endoscopic examination may show infarcts and ulcers throughout the GI tract. The most common cause of death in Degos disease is microvascular infarctions in the intestines, resulting in perforation and peritonitis. Cutaneous lesions typically precede visceral symptoms and have a characteristic appearance described as porcelain-white, atrophic, umbilicated papules with erythematous or telangiectatic borders. There is no known treatment for this disease and it is usually fatal.

Dermatologic Diseases

The skin and the GI tract may be affected concurrently by the same processes. Although many dermatologic diseases can manifest with involvement of the GI tract, 3 with notable GI

manifestations are epidermolysis bullosa, lichen planus, and mastocytosis. (Mastocytosis is discussed in the Hematologic Disorders section of this chapter.)

Epidermolysis Bullosa

Epidermolysis bullosa is an inherited disorder characterized by the development of trauma-induced blisters with resultant scarring. It results from mutations of genes encoding for structural proteins located at the dermal-epidermal junction. Disruption in these structural proteins results in mechanical fragility of the skin and other epithelialized organs. It is important for the gastroenterologist to be aware of this condition because it may lead to poor dentition, dysphagia from esophageal strictures, malabsorption, severe constipation, and anal fissures. Minor trauma from food boluses leads to bullae, ulceration, and scarring of the esophageal mucosa with formation of strictures, most commonly in the proximal esophagus. Supportive therapy is the mainstay of treatment of epidermolysis bullosa. Minimizing trauma with a soft diet, attention to wound care, and adequate nutritional support are paramount. Antireflux measures and antisecretory medication may help to minimize esophageal injury. It is important to be aware of the risk of mucosal trauma from endoscopic procedures. Esophageal strictures from epidermolysis bullosa are usually dilated with balloons rather than bougies to avoid shearing forces associated with bougies.

Lichen Planus

Lichen planus is a mucocutaneous, autoimmune, inflammatory disease that most frequently involves the skin and oral mucosa. Because lichen planus is a disease that affects squamous mucosa, it can also involve the esophagus. Esophageal lichen planus is predominantly a disease of women. Symptomatic esophageal involvement may be the initial manifestation of the disease, and solid food dysphagia of variable severity is the predominant symptom of esophageal disease. There is typically a long delay in diagnosis, often preceded by multiple endoscopies, dilations, and treatment of reflux.

A proximal esophageal stricture is the most common finding, although variations of esophageal disease include distal strictures, multiple rings, and long esophageal strictures with a small-caliber esophagus (Figure 13.1) that is radiologically identical to eosinophilic esophagitis. Common endoscopic findings include difficult passage of the endoscope through the proximal esophagus on initial esophageal intubation, mucosal thickening with superficial ulceration, mucosal sloughing, and rings (Figure 13.2). Mucosal sloughing is often evident on initial passage of the endoscope or on withdrawal. This shearing off of friable epidermis from minor endoscopic trauma has been termed an endoscopic Koebner phenomenon with a predilection for disease to flare in sites of trauma. Therefore, although esophageal dilation is often a necessary treatment to relieve dysphagia, unnecessary dilatations actually might cause a disease flare, particularly if done without concurrent therapies aimed at controlling the disease.

Given reports of a significant association between lichen planus and infection with hepatitis C virus, hepatitis C virus serologic testing should be considered for all affected patients. An increased risk of squamous cell carcinoma has been described with lichen planus; however, there are no recommendations for cancer screening of patients who have esophageal lichen planus, although the co-occurrence should be entertained. The diagnosis of esophageal lichen planus should be considered for patients with refractory strictures, particularly middle-aged women, with or without known lichen planus.

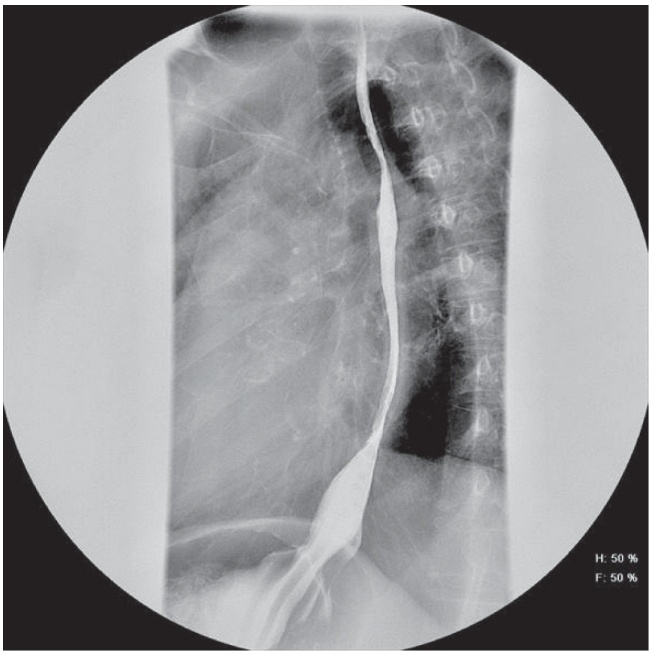

Figure 13.1. Radiographic Findings in Lichen Planus of the Esophagus. Esophogram shows diffuse esophageal narrowing and areas of more focal narrowing.

Hematologic Disorders

Amyloidosis

Amyloidosis is characterized by the extracellular deposition of an abnormal fibrillar protein, which disrupts tissue structure and function. Amyloidosis can be acquired or hereditary, and systemic or localized to 1 or more organs, such as the liver or the GI

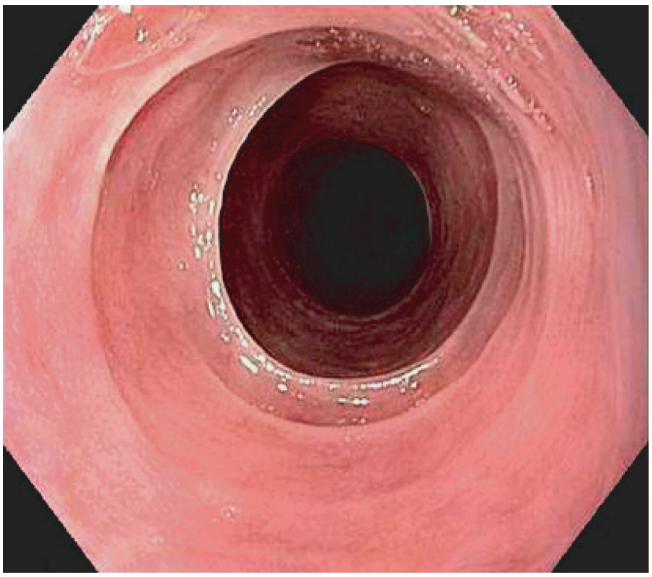

Figure 13.2. Endoscopic Findings in Esophageal Lichen Planus. Endoscopic examination shows multiple, thin, membranous webs and luminal narrowing.

tract. Amyloidosis is classified according to the type of precursor protein. The 2 major types of amyloidosis with clinically important GI involvement are primary and secondary amyloidosis. In primary or AL amyloidosis, the protein fibrils are composed of fragments of monoclonal light chains; in reactive (secondary) or AA amyloidosis, the protein fibrils are composed of fragments of the circulating acute-phase reactant serum amyloid A protein.

GI disease in amyloidosis results from either mucosal infiltration or neuromuscular infiltration. Within the GI tract, the most common sites of infiltration are the descending duodenum (100%), the stomach and colorectum (>90%), and the esophagus (70%). Mucosal infiltration by amyloid causes polypoid protrusions, erosions, ulcerations (Figure 13.3), mucosal friability, and wall thickening.

Characteristic endoscopic findings in AL amyloidosis include submucosal hematomas and hemorrhagic bullous colitis. Neuromuscular infiltration initially affects the intrinsic enteric nervous system, resulting in a neuropathic process characterized by normal amplitude but uncoordinated contractions. In more advanced disease, tissue wall infiltration causes a myopathic process with low-amplitude contractions.

Symptomatic patients with GI amyloidosis have 4 major presentations: GI bleeding, chronic intestinal dysmotility, malabsorption, and protein-losing gastroenteropathy (Box 13.2). Less common GI manifestations include intestinal obstruction from amyloid masses, called amyloidomas, and cholangitis from amyloid deposition around the ampulla of Vater, resulting in biliary obstruction. Liver involvement is common in both AL amyloidosis and AA amyloidosis. Common symptoms with hepatic amyloidosis include weight loss, fatigue, and abdominal pain. The majority of patients have hepatomegaly, with an elevated serum alkaline phosphatase level being the most frequent abnormal liver test result.

The diagnosis of GI amyloidosis can be challenging in patients without an established diagnosis of amyloidosis. It is important to maintain a high degree of awareness when patients have disorders known to be associated with amyloidosis, such as multiple myeloma and chronic inflammatory disorders. When AL amyloidosis is suspected, testing should be done to assess for the presence of serum or monoclonal proteins. However, diagnostic confirmation of GI involvement requires tissue biopsy of duodenal or colorectal mucosa, which is more sensitive than a subcutaneous fat biopsy. Treatment of amyloid-related GI complications is directed toward symptom control and the underlying cause of amyloidosis.

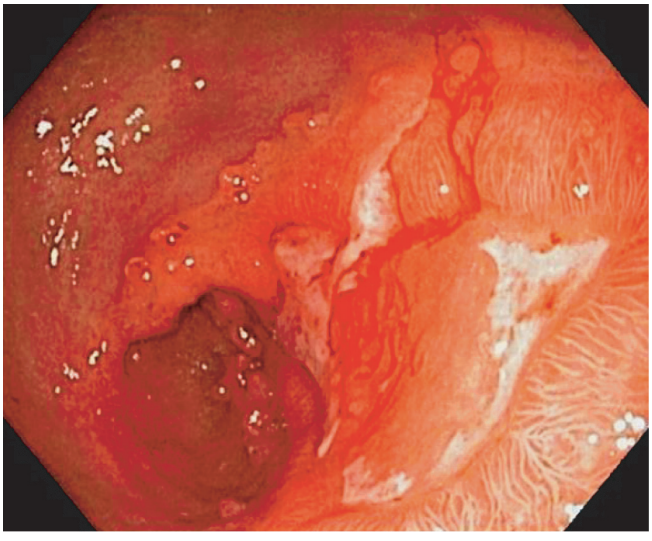

Figure 13.3. Amyloid Ulcer. This large amyloid ulcer with surrounding polypoid mucosa was located in the gastric antrum.

Box 13.2. Four Major Syndromic Presentations of Symptomatic Patients With Gastrointestinal Amyloidosis

1. *Gastrointestinal bleeding*—secondary to vascular fragility, mucosal lesions, or ischemia
2. *Intestinal dysmotility*—causing dysphagia, gastroparesis, chronic intestinal pseudo-obstruction, constipation, bacterial overgrowth, or bile acid malabsorption
3. *Malabsorption*—due to mucosal infiltration
4. *Protein-losing gastroenteropathy*—should be considered in patients with hypoalbuminemia and edema

Porphyria

Porphyria results from a deficiency in 1 of the enzymes involved in the heme synthetic pathway. The porphyrias are commonly classified by clinical features into 2 main groups: acute porphyrias and cutaneous porphyrias. The *acute porphyrias* are characterized by dramatic and potentially life-threatening neurologic symptoms, whereas the *cutaneous porphyrias* have no neurologic symptoms but instead manifest with severe skin lesions.

The 4 acute porphyrias are acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and aminolevulinic acid (ALA) dehydratase deficiency porphyria. Acute intermittent porphyria is the most common acute porphyria. Patients with any of the 4 acute porphyrias can present with acute neurovisceral attacks consisting of severe abdominal pain, nausea and vomiting, constipation, tachycardia, paresthesias, weakness, dark urine, and peripheral sensory deficits. Factors that commonly precipitate an episode of acute porphyria include certain medications, alcohol ingestion, smoking, fasting, infections, and pregnancy.

Acute intermittent porphyria is inherited in an autosomal dominant manner and is associated with increased levels of ALA and porphobilinogen; there are no skin findings. Variegate porphyria is characterized by increased levels of urine coproporphyrin and stool protoporphyrin and coproporphyrin; patients can have skin disease, with or without an abdominal attack. In hereditary coproporphyria, stool and urine coproporphyrin levels are increased; skin disease can be present, usually with an abdominal attack. In the very rare ALA dehydratase deficiency porphyria, only the ALA level is increased; there are no skin findings, and the condition is autosomal recessive. Urine ALA and porphobilinogen levels are always increased *during* an acute abdominal crisis (ALA accumulates in the absence of ALA dehydratase). In acute intermittent porphyria, urine ALA and porphobilinogen values usually are increased *between* attacks.

The most common cutaneous porphyria is porphyria cutanea tarda, which affects only the skin and is associated with high alcohol intake, iron overload states such as hereditary hemochromatosis, hepatitis C virus infection, and systemic illnesses including systemic lupus erythematosus (SLE), diabetes mellitus (DM), and chronic kidney disease. Excess porphyrins, which are photoreactive, are deposited in the dermis, causing tissue damage that manifests as vesicles and bullae.

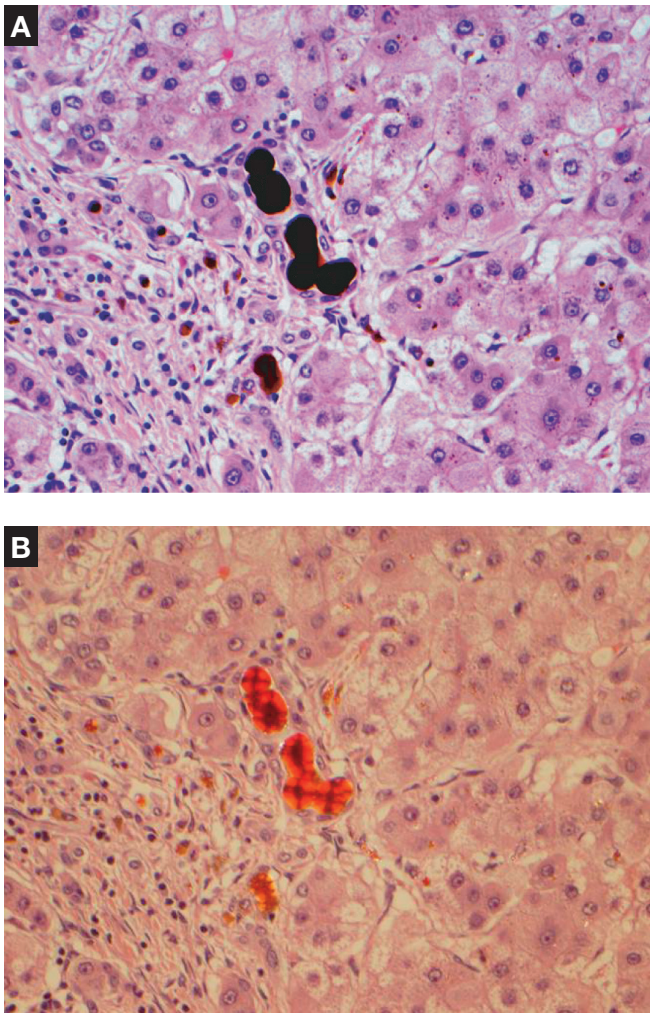

Figure 13.4. Erythropoietic Protoporphyria. A, Liver biopsy specimen shows distorted lobular architecture with red-brown protoporphyrin pigment in hepatocytes and lumen of bile canaliculi (hematoxylin-eosin, original magnification ×200). B, Polarizing microscopy shows characteristic bright red and centrally located Maltese cross appearance of globular protoporphyrin deposits (hematoxylin-eosin, original magnification ×200).

The second most common cutaneous porphyria is erythropoietic protoporphyria, with exquisite photosensitivity being its principal clinical manifestation. In addition, in 10% of patients, clinically evident liver disease (cirrhosis and liver failure) results from progressive hepatic accumulation of protoporphyrin (Figure 13.4). In patients with erythropoietic protoporphyria, liver disease typically occurs after age 30 years; the urine is notable in lacking porphyrin metabolites, which are detected only in the stool. The diagnosis of acute porphyria should be considered if patients have recurrent episodes of severe abdominal pain, constipation, dark urine, and neuropsychiatric disturbances, while the diagnosis of cutaneous porphyria should be considered if patients have typical dermatologic findings.

Management of an acute porphyric attack consists of quickly identifying and reversing the precipitating factors. Acetaminophen, meperidine, and morphine can be used safely for pain management. Ondansetron is the preferred antiemetic, and use of promethazine should be avoided. Intravenous glucose is beneficial. The definitive treatment of an acute porphyric attack is intravenous hemin, which replenishes the depleted heme pool and ameliorates signs and symptoms of the acute porphyric attack.

Systemic Mastocytosis

Mastocytosis refers to the infiltration of mast cells in the skin or various other organs. Cutaneous mastocytosis is the most common form; however, the spectrum of disease includes symptoms related to the release of mast cell mediators (eg, histamine) and signs resulting from multiorgan mast cell infiltration, including infiltration of the liver and intestines. The characteristic dermatologic lesion is urticaria pigmentosa, which manifests as yellow-tan macules involving the extremities and trunk, with the classic finding of Darier sign (urticaria after scratching). GI manifestations of systemic mastocytosis are varied and include nausea, vomiting, diarrhea, and abdominal pain. Hyperhistaminemia can result in gastric acid hypersecretion and peptic ulcer disease. Infiltration of the liver causes hepatomegaly, liver test abnormalities, and portal hypertension. Systemic mastocytosis is a clonal disorder of mast cell progenitors and is associated with activating mutations of the *c-kit* gene. However, the tyrosine kinase inhibitors, such as imatinib mesylate, are rarely effective in systemic mastocytosis because the most common mutation interferes with drug binding.

Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive abnormality of the β-globin chain of hemoglobin that results in poorly deformable, sickled red blood cells that cause microvascular occlusion and hemolytic anemia. The spleen is nearly always involved in SCD, with hyposplenism or asplenism resulting from splenic infarction. Patients with splenic infarction present with left upper quadrant pain, nausea and vomiting, a friction rub over the splenic area, and leukocytosis. Splenic atrophy predisposes to infection with encapsulated bacteria. Liver and GI complications are common in SCD.

Several different acute and chronic processes can involve the liver in SCD. Acute processes include liver infarction, acute sickle hepatic crisis, acute hepatic sequestration, sickle cell intrahepatic cholestasis, and liver abscesses. Chronic liver disease in SCD may be due to hemosiderosis, chronic viral hepatitis, or nodular regenerative hyperplasia.

Patients with acute liver processes in SCD most commonly present with right upper quadrant pain and acute painful hepatomegaly. High blood viscosity in SCD predisposes to liver infarction despite the dual blood supply of the liver. Acute sickle hepatic crisis affects 10% of patients with a painful vasoocclusive crisis and simulates acute cholecystitis with fever, right upper quadrant pain, leukocytosis, and variable elevations in liver enzymes. The liver is usually enlarged and tender in acute sickle hepatic crisis. Acute hepatic sequestration with jaundice is accompanied by a decrease in hemoglobin and is due to obstruction of sinusoidal blood flow by masses of sickled erythrocytes in the liver.

Sickle cell intrahepatic cholestasis is a rare but potentially fatal complication representing an unusually severe hepatic crisis from widespread sickling in the hepatic sinusoids, resulting in hepatic ischemia. It is characterized by extreme hyperbilirubinemia, with the conjugated fraction greater than 50% of the total bilirubin. Patients with sickle cell intrahepatic cholestasis die of liver failure.

Liver abscesses are more common in SCD due to asplenism and an impaired reticuloendothelial system. SCD patients have a notable predisposition to liver abscesses due to *Yersinia enterocolitica* infection because of iron overload and deferoxamine therapy, which are 2 conditions that increase susceptibility to this organism.

Iron overload may cause chronic liver disease in SCD and is related to accumulation of transfused iron and continuous hemolysis. Chronic hepatitis C is more prevalent in SCD patients who received transfusions before blood products were screened (June 1992).

Nodular regenerative hyperplasia may occur in SCD and is characterized by nodules of regenerative hepatocytes distributed diffusely throughout the liver, with atrophy of the intervening parenchyma (Figure 13.5). Lack of fibrosis and hepatic dysfunction differentiate it from cirrhosis. Nodular regenerative hyperplasia is believed to result from an obstructive portal venopathy and can be seen with hematologic disorders, rheumatologic conditions, and side effects of certain medications (eg, azathioprine).

GI complications of SCD include cholelithiasis, abdominal crisis, acute pancreatitis, peptic ulcer disease, and ischemic bowel. The gallstones in SCD are typically of the black pigment type as a result of elevated bilirubin excretion. They are commonly seen on plain radiographs because the bilirubin is in the form of a calcium salt. There is an increased incidence of choledocholithiasis and its associated complications. Cholecystectomy is the most frequent surgical procedure in patients with SCD, and some experts advocate early cholecystectomy in asymptomatic patients. In an acute vasoocclusive crisis, small infarcts occur in the mesentery and abdominal viscera causing severe abdominal pain and signs of peritoneal irritation with radiographic evidence of ileus. The crisis may mimic other acute abdominal processes but usually resolves with supportive care. Acute pancreatitis related to SCD may result from microvascular occlusion and ischemic injury. Peptic ulcer disease is more common in SCD and may be due to reduced mucosal resistance from ischemia. Ischemic bowel due to intravascular sickling, causing microvascular occlusion, is an uncommon complication of SCD.

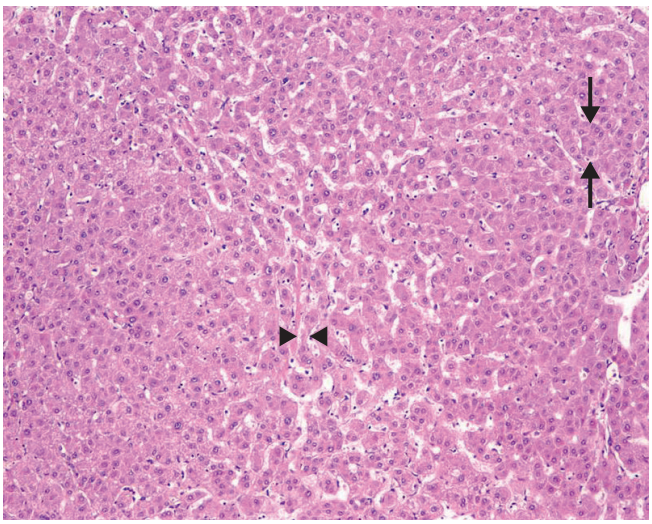

Figure 13.5. Nodular Regenerative Hyperplasia. Liver biopsy specimen shows atrophy of zone 3 hepatocytes (arrowheads) and hypertrophy of zone 1 hepatocytes (arrows) without fibrosis (hematoxylin-eosin, original magnification ×100).

Pulmonary Disorders

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder resulting from mutations in the CF transmembrane regulator (*CFTR*) gene. The *CFTR* gene encodes for a chloride channel protein in the apical surface of epithelial membranes. Dysfunction of *CFTR* results in altered electrolyte content in the environment external to the surface epithelial membranes, with dessication and reduced clearance of secretions from tubular structures lined by affected epithelia. The pulmonary manifestations of CF are the most serious because they lead to respiratory failure. However, the CFTR protein is found throughout all GI tract epithelia, including the small intestine, pancreas, and hepatobiliary system. Therefore, *CFTR* dysfunction can result in many GI complications, including meconium ileus, pancreatic insufficiency, pancreatitis, gastroesophageal reflux disease, distal intestinal obstruction syndrome (DIOS), constipation, small intestinal bacterial overgrowth (SIBO), and liver disease. Since over half of patients with CF in the United States are adults, it is important to be able to recognize and manage the GI complications of CF.

The GI manifestations of CF begin in infancy, with the earliest manifestation being meconium ileus, a neonatal bowel obstruction. It is the presenting symptom in 15% of infants with CF, and it classically manifests with signs of intestinal obstruction within 48 hours of birth. Characteristic radiographic findings show distended loops of bowel devoid of air-fluid levels. Acetylcysteine (Mucomyst), a mucolytic, is a safe and effective treatment to dissolve and dislodge meconium. Meconium-induced obstruction is also treated with diatrizoate (Gastrografin) enemas. Complicated meconium ileus requires surgical therapy.

Pancreatic insufficiency is the most common GI complication of CF. It often develops early in life with the more severe *CFTR* gene mutations. Pancreatic insufficiency leads to maldigestion and malabsorption of nutrients. Long-term sequelae of malnutrition include growth retardation, cognitive dysfunction related to vitamin E deficiency, and more rapid decline in pulmonary function. A 72-hour stool collection to measure fecal fat can be performed to screen for pancreatic insufficiency. Patients with pancreatic insufficiency require lifelong pancreatic enzyme replacement therapy. Fibrosing colonopathy is a severe intestinal fibrostenotic process that occurred in CF patients who ingested large doses of pancreatic enzyme replacement therapy; because of this complication, the recommended upper limit is 2,500 lipase units per kg per meal.

Acute pancreatitis, which develops in 10% of CF patients with preserved pancreatic function, occurs when there is decreased ductal flow from inspissated secretions leading to premature activation of trypsinogen and local inflammation. Treatment of recurrent acute or chronic pancreatitis in patients with CF is similar to treatment in those without CF. Intravenous fluids are the cornerstone of management; however, use of narcotic analgesics should be minimized because they can precipitate constipation and DIOS (see below).

Gastroesophageal reflux disease occurs in approximately 30% of adult CF patients. The basic mechanism, transient lower esophageal sphincter relaxation, is the same in CF patients as in healthy controls. However, transient lower esophageal sphincter relaxations cause more frequent and more proximal reflux events in CF patients. Proton pump inhibitors are the first-line therapy for gastroesophageal reflux disease in CF patients. Lung function improves in CF patients treated with gastric acid suppression.

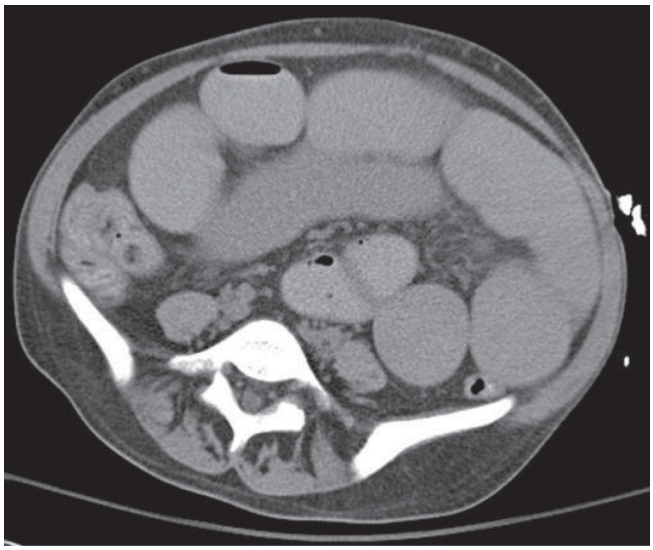

Figure 13.6. Distal Intestinal Obstruction Syndrome of Cystic Fibrosis. Computed tomographic image shows dilated loops of fluid-filled small bowel throughout the abdomen and pelvis with fecalization of bowel contents and gradual tapering of small-bowel caliber in the distal ileum.

DIOS, a unique feature of CF, is characterized by partial or complete fecal obstruction of the ileocecal region. It occurs in CF patients of all ages, including adults, and results from accumulation of viscous fecal material with adherence to the mucosa. Patients with DIOS present with acute or chronic intestinal obstruction with abdominal pain and distention. They may continue to have stool output. On physical examination, a right lower quadrant mass may be palpable. Radiographic imaging typically shows fecal loading in the right lower quadrant as evidenced by a bubbly-granular fecal mass (Figure 13.6). DIOS can be diagnosed from clinical symptoms, physical findings, and suggestive radiographic imaging. Management of DIOS includes surgical consultation, nil per os, nasogastric tube decompression, and intravenous fluids. In cases of complete obstruction, a hyperosmolar contrast enema such as diatrizoate should be administered to clear the impacted fecal mass. Hyperosmolar agents cause luminal hydration with resultant mobilization of the mucus-stool mass and relief of obstruction. With partial bowel obstructions, lavage with oral polyethylene glycol solutions and oral laxatives can be effective. Surgical intervention remains the last resort when medical management fails or bowel ischemia develops. After recovery from an episode, prevention of recurrent episodes of DIOS with routine use of osmotic agents such as polyethylene glycol is critical.

Constipation is a frequent symptom in CF and, like DIOS, is related to decreased water secretion caused by the *CFTR* defect. In contrast to DIOS, which is an obstructive process that starts at the terminal ileum and extends *distally*, constipation in CF patients is an obstructive process that begins in the sigmoid colon and extends *proximally*. Osmotic laxatives are the first-line treatment of CF-related constipation.

SIBO is seen in up to 50% of CF patients. Thick mucous secretions, intestinal dysmotility, and the use of acid-suppressing medications predispose CF patients to the development of SIBO. Diagnostic tests, such as culture of duodenal aspirates and breath hydrogen testing, have limitations. Empirical therapy with antibiotics is frequently performed for SIBO.

CF-related liver disease is becoming a more prevalent complication. There is a broad spectrum of hepatobiliary disease in CF, which includes microgallbladder, cholelithiasis, hepatic steatosis, nodular regenerative hyperplasia, and focal biliary cirrhosis with portal hypertension. Notably, asymptomatic elevation in serum liver enzymes or hepatosplenomegaly may be the only clinical manifestations of CF-related liver disease.

The treatment of symptomatic liver disease in CF is a challenge and depends on the age of the patient and the extent of the liver disease. Cholestatic liver disease is best treated with ursodeoxycholic acid (15-20 mg/kg daily), and treatment should be initiated with early recognition of CF-related liver disease to improve the biochemical profile, facilitate biliary drainage, and delay progression of liver disease.

In addition to the CF-related GI and liver complications, several GI diseases, including celiac disease and GI cancer, are associated with CF. The prevalence of celiac disease is higher in CF patients than in the general population. It is important to recognize that tissue transglutaminase immunoglobulin A can be elevated in CF patients even in the absence of histologic evidence of active celiac disease. Hence, the diagnosis of celiac disease should not be made solely on the basis of positive IgA tissue transglutaminase serology and requires compatible small intestinal histologic changes and response to a gluten-free diet. Compared with the general population, patients with CF are at increased risk for esophageal, gastric, hepatobiliary, gallbladder, small intestinal, and colon cancers. Although the relative risk of GI cancer is increased in CF, the absolute risk is small. There are no formal consensus recommendations to screen for malignancies in CF patients; however, it is important to maintain a high degree of awareness for GI cancers, especially when GI symptoms persist in older CF patients.

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease that commonly involves the lungs and less frequently involves the liver and GI tract. Symptomatic liver involvement is infrequent. Most patients have only biochemical liver test abnormalities, most commonly an elevated alkaline phosphatase level. However, in a small percentage of patients, progressive liver disease develops, including cholestasis, hepatitis, and nodular regenerative hyperplasia with resultant portal hypertension. In addition, portal vein thrombosis may occur because of stasis from obliteration of small portal veins by granulomatous phlebitis. Budd-Chiari syndrome may develop from extrinsic compression of hepatic veins by enlarged granulomatous lymph nodes.

In contrast to sarcoidosis involvement of the liver, sarcoidosis of the GI tract is rare, with the stomach being the most commonly involved portion of the GI tract. Patients with gastric sarcoidosis most commonly present with postprandial epigastric pain related either to peptic ulceration or to gastric luminal narrowing from granulomatous inflammation and fibrosis of the gastric wall. Patients may initially present with massive GI hemorrhage from ulceration. Endoscopic findings in gastric sarcoid include ulcerations, thickened gastric folds, mucosal polyps or nodules, and antral deformities. A characteristic finding on upper GI series is a resemblance to linitis plastica because of granulomatous involvement of the gastric wall. Involvement of other portions of the GI tract by sarcoidosis is much less common. Patients with esophageal involvement may present with dysphagia related to either dysmotility or mechanical obstruction. Patients with sarcoidosis of the small intestine may present with abdominal pain, diarrhea, malabsorption, or protein-losing enteropathy. Colonic involvement manifests with polypoid lesions, stenosis, and ulceration.

Pancreatic sarcoidosis may simulate carcinoma with a mass in the head of the pancreas and associated obstructive jaundice and weight loss. The majority of patients with pancreatic sarcoidosis have bilateral hilar adenopathy.

The diagnosis of hepatic and luminal GI tract sarcoidosis is made by the presence of noncaseating granulomas on biopsy, extra-abdominal organ involvement, and exclusion of granulomatous infections. The differential diagnosis of GI sarcoidosis includes Crohn disease, foreign body reaction, tuberculosis, histoplasmosis, and syphilis. At times, sarcoidosis coexists with Crohn disease or ulcerative colitis. Treatment of GI sarcoidosis depends on the severity and extent of the disease, with asymptomatic patients requiring no treatment. Corticosteroids and other immunosuppressive agents are the treatment of choice for symptomatic patients.

Obstructive Sleep Apnea

Obstructive sleep apnea is an underrecognized cause of hepatic ischemia.

Immunologic Disorders

Angioedema

Angioedema affecting the intestinal tract causes severe abdominal pain with vomiting due to edematous bowel obstruction. Intestinal angioedema results from hereditary, acquired, or drug-induced causes. Hereditary angioedema is an autosomal dominant disorder characterized by quantitative or functional deficiency of C1 esterase inhibitor, which inhibits complement proteases and coagulation system proteases. C1 esterase inhibitor deficiency results in unregulated activation of the complement and coagulation systems and increased levels of bradykinin, which is responsible for angioedema. Hereditary angioedema is associated with localized swelling involving all layers of the skin or walls of hollow organs such as in the respiratory or GI tracts. GI manifestations include nausea, vomiting, abdominal pain, diarrhea, and ascites. Orthostatic symptoms may occur as a result of fluid shifts into the intestinal lumen or peritoneal cavity, which decrease the effective circulating volume. Symptoms are at maximum intensity for approximately 24 hours and can resolve spontaneously. Imaging may show edematous bowel (Figure 13.7) and ascites.

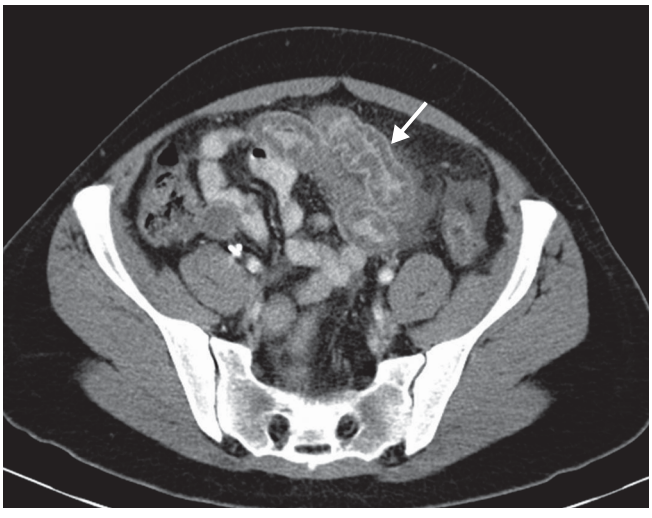

Figure 13.7. Mesenteric Angioedema. Computed tomographic image shows thickened small-bowel loop (arrow).

Measurement of C4 levels is a cost-effective screening test to rule out hereditary angioedema because virtually all patients with hereditary angioedema have a persistently low C4 level. Subsequent measurement of quantitative and functional levels of C1 esterase inhibitor confirms the diagnosis. Treatment with attenuated androgens to stimulate C1 esterase inhibitor biosynthesis can prevent attacks, and C1 esterase inhibitor concentrate or fresh frozen plasma can be administered during attacks to restore normal C1 esterase inhibitor levels.

Intestinal angioedema may be acquired, with C1 esterase inhibitor deficiency related to collagen vascular diseases or lymphoproliferative disorders. Angiotensin-converting enzyme inhibitors can cause angioedema of the intestine, independently of diminished complement or C1 esterase inhibitor levels. Angiotensin II receptor antagonists and renin inhibitors have also been implicated. Women taking medications containing estrogen may present with similar clinical manifestations.

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder characterized by impaired B-lymphocyte maturation with hypogammaglobulinemia. T-lymphocyte dysfunction is variably seen in CVID. It is estimated to affect 1 in 25,000 individuals; age at onset is typically after puberty and before 30 years. Affected individuals have recurrent respiratory infections, autoimmune phenomena, and increased rates of malignancy. GI manifestations of CVID are seen in up to 50% of individuals and include atrophic gastritis, chronic diarrhea, nodular lymphoid hyperplasia, and GI malignancies. Gastric manifestations of CVID include atrophic gastritis and achlorhydria, with the development of pernicious anemia being common. The risk of gastric carcinoma is markedly elevated in patients with CVID, with concomitant *Helicobacter pylori* infection further increasing the risk. The most common GI manifestation of CVID is chronic diarrhea, which can be secondary to several conditions including GI infections, a spruelike disorder, SIBO, inflammatory bowel disease, or small intestinal lymphoma.

Chronic giardiasis is the characteristic GI infection of CVID. It may cause refractory diarrhea, malabsorption, and weight loss. Other GI infections causing diarrhea in CVID include cytomegalovirus infection and cryptosporidiosis.

A spruelike syndrome that occurs in CVID is distinct from celiac disease since it does not respond to a gluten-free diet. The absence of plasma cells in the lamina propria is a specific histologic feature that helps to distinguish CVID from other small intestinal enteropathies. Some patients with spruelike intestinal changes benefit from treatment with corticosteroids.

Liver disease with significant hepatic dysfunction occurs in approximately 10% of CVID patients. The most common cause of liver dysfunction is nodular regenerative hyperplasia.

Initial evaluation of patients with CVID includes measurement of immunoglobulin levels and demonstration of an impaired response to vaccination. Referral to a clinical immunologist is indicated to determine the most appropriate therapies and to help monitor the patient for associated disorders.

Selective IgA Deficiency

Selective IgA deficiency is the most common primary immunodeficiency disorder, occurring in about 1 in 500 persons. It is characterized by selective loss of secretory and serum IgA. Individuals are susceptible to respiratory, urogenital, and GI

infections (especially giardiasis). Celiac disease and pernicious anemia occur with increased frequency in patients with selective IgA deficiency.

Renal Diseases and Hemodialysis

Chronic Kidney Disease

Chronic kidney disease can be complicated by dysgeusia, anorexia, nausea, vomiting, esophagitis, gastritis, angiodysplasias of the GI tract, peptic ulcer disease, duodenitis, duodenal pseudomelanosis (asymptomatic), abdominal pain, constipation, pseudo-obstruction, perforated colonic diverticula, small-bowel and colonic ulceration, intussusception, GI tract bleeding, amyloidosis, diarrhea, fecal impaction, and SIBO.

Hemodialysis

In patients undergoing hemodialysis, a refractory exudative ascites of unclear pathogenesis can develop; this resolves with renal transplant. These patients also have a greater risk of ischemic colitis. Infections and ulcerative complications of the GI tract, diverticulitis, and perforated colonic diverticula often develop in patients who have had renal transplant.

Peritoneal Dialysis

Patients undergoing continuous ambulatory peritoneal dialysis are at increased risk of bacterial peritonitis and a rare but serious complication, encapsulating peritoneal sclerosis (EPS). EPS is characterized by partial or intermittent bowel obstruction accompanied by marked sclerotic thickening of the peritoneal membrane. The bowel loops within the sclerotic membrane become adherent and encapsulated, leading to bowel obstruction. A typical computed tomographic feature of EPS is an enhancing thickened peritoneum, which may progress to peritoneal encapsulation of the involved bowel loops and is frequently described as "cocooning." Tamoxifen has been successful in decreasing EPS-related fibrosis and improving intestinal function.

Polycystic Kidney Disease

The adult form (autosomal dominant) of polycystic kidney disease is associated with hepatic cysts, choledochal cysts, congenital hepatic fibrosis, and Caroli disease. The frequency of hepatic cysts increases with age, and large cysts are more common in women. Despite large cysts, liver function is preserved. Complications of hepatic cysts include infection and biliary obstruction, which requires antibiotic treatment and percutaneous drainage.

Endocrine Disorders

Diabetes Mellitus

GI symptoms are common in patients with DM. Autonomic neuropathy complicating DM can involve the entire GI tract. Dysphagia from esophageal dysmotility occurs as the result of vagal dysfunction. Esophageal stasis can predispose to *Candida* infection, and new-onset odynophagia in a diabetic patient should suggest the presence of *Candida* esophagitis. Gastroparesis is a common complication of poorly controlled DM. Symptoms include early satiety, bloating, heartburn, nausea, and intermittent vomiting. A succussion splash may be appreciated on physical examination. Phase III of the migrating motor complex is frequently absent, which predisposes to the formation of gastric bezoars. Diarrhea and fecal incontinence are frequent complaints in DM. The diarrhea is often watery and nocturnal. Intestinal autonomic neuropathy may be the cause; however, other conditions to consider include celiac disease (more prevalent in type 1 DM), pancreatic exocrine insufficiency, and SIBO. Severe constipation associated with colonic dysmotility occurs in 20% of diabetic patients with neuropathy. Fecal incontinence is commonly due to anal sphincter dysfunction and decreased rectal sensation. Fatty liver disease is a frequent occurrence.

Thyroid Disease

Hyperthyroidism may manifest as hyperphagia, weight loss, mild diarrhea, steatorrhea, abdominal pain, vomiting, concomitant atrophic gastritis, dysphagia, ascites, jaundice, and nonspecific mild abnormalities on liver function testing. Autoimmune hepatitis and primary biliary cirrhosis also may be associated disorders. Hypothyroidism often results in anorexia, weight gain, constipation, dysphagia, heartburn, and, less often, intestinal pseudo-obstruction, achlorhydria, and ascites (high concentration of total protein and high serum-ascites albumin gradient). Associated GI diseases include pernicious anemia, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis, and celiac disease.

Parathyroid Disease

Hyperparathyroidism, with hypercalcemia, classically produces anorexia, nausea, vomiting, constipation, and abdominal pain; rarely, peptic ulcer disease and pancreatitis develop. Patients with hypoparathyroidism can present with diarrhea, steatorrhea, abdominal pain, pseudo-obstruction, protein-losing enteropathy, and lymphangiectasia; also, autoimmune hepatitis may develop.

Oncologic Disorders

Leukemias and lymphomas commonly involve the GI tract and liver. Hodgkin disease can involve the liver, extrahepatic bile ducts, or lymph nodes, or it can manifest as intrahepatic cholestasis without hepatobiliary involvement. Unusual tumors affecting the gut include alpha chain disease (also called immunoproliferative small intestine disease), which diffusely infiltrates the small intestine and adjacent lymph nodes (B cells and α heavy chains are produced in excess); mantle cell lymphomas, which mimic a multiple polyposis syndrome; multiple myeloma or amyloidosis, with focal plasmacytomas (mass, ulceration, bleeding, or obstruction), GI mucosal infiltration with malabsorption, or hyperviscosity syndrome (ischemia); Waldenström macroglobulinemia, with GI tract and hepatosplenic infiltration and malabsorption; and small cell lung carcinoma and other malignancies, with paraneoplastic pseudo-obstruction (patients may be positive for antineuronal nuclear antibody, type 1 Purkinje cell antibody, or N-type calcium channel–binding antibody).

Allogenic bone marrow transplant often is complicated by graft-versus-host disease (GVHD). Usually occurring in the first 20 to 80 days after transplant, *acute GVHD* is characterized by erythematous maculopapular rashes, small and large intestinal mucosal involvement (diarrhea, protein-losing enteropathy, malabsorption, pain, bleeding, and apoptotic bodies seen in biopsy specimens, even in areas that appear normal on endoscopy), and cholestatic liver disease. Usually occurring 80 to 400 days after

transplant (and usually in persons with previous acute GVHD), *chronic GVHD* is characterized by cholestatic liver disease (vanishing bile ducts), esophageal disease (dysphagia, strictures, and webs), small-bowel disease (diarrhea or bacterial overgrowth), skin disease, and polyserositis. Venoocclusive disease of the liver, with bland, nonthrombotic obliteration of small hepatic veins and venules due to conditioning therapy (radiotherapy or chemotherapy), usually occurs 8 to 23 days after transplant.

Neuromuscular Disorders

Many neurologic and muscular disorders affect the GI tract. Acute head injury with intracranial hypertension, like many other serious illnesses, can result in stress gastritis. However, deep ulceration, sometimes with perforation, can occur with acute head injury, apparently as a result of vagal stimulation of gastrin and gastric acid production. Similar ulceration can occur after burns that cover a large surface area of the body. Abdominal pain, nausea, and vomiting rarely are attributed to migraine or temporal lobe epilepsy (temporal lobe epilepsy often includes central nervous system symptoms). Patients with cyclic vomiting may present with recurrent attacks of abdominal pain, nausea, and vomiting. Some persons with this disorder find relief with hot showers or baths and recover with cessation of the use of marijuana. Cerebrovascular disease and cerebral palsy commonly result in oropharyngeal dysphagia due to dysmotility.

Multiple sclerosis frequently affects the GI tract with oropharyngeal dysphagia, gastroparesis, constipation, or disorders of defecation or fecal incontinence. Patients with Parkinson disease often have oropharyngeal dysphagia, gastroesophageal reflux disease, esophageal dysphagia, constipation, and fecal incontinence. Both amyotrophic lateral sclerosis and myasthenia gravis can cause oropharyngeal dysphagia.

More diffuse GI tract dysmotility syndromes occur with poliomyelitis, Huntington chorea, dysautonomia syndromes, Shy-Drager syndrome, Chagas disease, and spinal cord injuries. Patients with dementia may be at risk for aspiration because of oropharyngeal dysphagia, and they may have weight loss because of decreased intake, poor diet, and pica.

Muscular dystrophies such as oculopharyngeal muscular dystrophy (third nerve palsy, often in persons who have French-Canadian ancestry) and Duchenne muscular dystrophy can be complicated by oropharyngeal dysphagia. Duchenne muscular dystrophy is associated with more widespread GI tract dysmotility.

Rheumatologic and Collagen Vascular Diseases

Scleroderma

Scleroderma is a chronic, connective tissue disease characterized by vascular damage and fibrosis of the skin and internal organs, including those in the GI tract. After skin involvement, the GI tract is the second most commonly involved organ system, with the esophagus being the most frequent segment involved. Involvement of the stomach, small intestine, colon, and anorectum is less common but may lead to severe complications and debility. The GI tract involvement is due to smooth muscle atrophy, fibrosis, small-vessel vasculitis, and neural damage. The esophagus is most frequently involved with smooth muscle atrophy and fibrosis of the distal two-thirds of the esophagus. Patients complain of dysphagia, heartburn, and regurgitation due to reflux and dysmotility. Most patients have Raynaud phenomena. Manometry classically shows an absence of peristaltic contractions and decreased lower esophageal sphincter pressure. Complications include strictures, Barrett esophagus, adenocarcinoma, and *Candida* esophagitis.

Replacement of the smooth muscle layers of the stomach by collagen leads to gastric hypomotility. In addition, a subset of scleroderma patients may have autonomic dysfunction affecting gastric emptying. Gastroparesis is reported to occur in up to 50% of patients and can result in significant morbidity and mortality. An additional gastric abnormality in scleroderma is gastric antral vascular ectasia.

The small intestine is frequently involved in scleroderma. Small intestinal complications include intestinal pseudo-obstruction, bacterial overgrowth, pneumatosis cystoides intestinalis, and perforation. Characteristic radiographic findings in cases of scleroderma pseudo-obstruction are dilatation of the small intestine and narrow valvulae conniventes, which remain tightly packed together despite the bowel dilatation and show the "hide-bound" bowel sign (Figure 13.8). This characteristic mucosal fold pattern in scleroderma is caused by bowel shortening from fibrosis of the longitudinal muscle layer, with a relative decrease in the distance separating the valvulae conniventes for a given degree of small-bowel dilatation.

The intestinal stasis from pseudo-obstruction may cause abdominal distention and pain, with bacterial overgrowth resulting in diarrhea, steatorrhea, malabsorption, and weight loss. Treatment of episodes of pseudo-obstruction complicated by bacterial overgrowth involves cycled antibiotics and octreotide. When used at low doses (25-50 mcg subcutaneously once nightly), octreotide stimulates small intestinal motility and is beneficial in patients with intestinal pseudo-obstruction and bacterial overgrowth. Despite these measures, many patients require home parenteral nutrition.

Pneumatosis cystoides intestinalis (PCI) is an uncommon condition characterized by multiple gas-filled cysts within the wall of the intestine. These cysts most commonly occur in the small bowel. PCI may be identified on plain radiographs or on

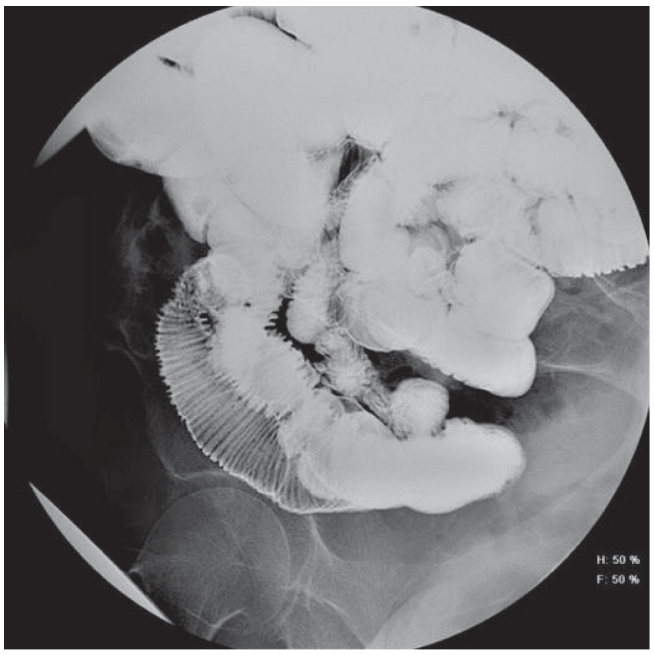

Figure 13.8. "Hide-Bound" Bowel Sign. The "hide-bound" bowel sign of scleroderma is seen in this small-bowel radiograph.

computed tomographic scans. PCI is not a disease and can be classified as either primary (idiopathic) or secondary. Scleroderma is a secondary cause of PCI. The cysts of PCI may rupture, resulting in benign, chronic pneumoperitoneum. Patients with benign chronic pneumoperitoneum do not have signs of peritonitis, and no therapy is required for this condition.

Lower GI symptoms from anorectal dysfunction are not infrequent in scleroderma. Scleroderma patients with impaired anorectal function may complain of various symptoms including constipation, diarrhea, urgency, and fecal incontinence. The 2 main complications of anorectal involvement by scleroderma are fecal incontinence and rectal prolapse. Fecal incontinence associated with scleroderma is multifactorial and includes diarrhea, decreased rectal compliance, and weakening of the internal anal sphincter. Deposition of collagen in the rectal wall likely contributes to the development of rectal prolapse by weakening the rectal submucosa. Rectal prolapse may further exacerbate the already reduced capacity and compliance of the rectum in scleroderma. Therefore, rectal prolapse should be sought in all scleroderma patients with fecal incontinence, particularly since it is a potentially treatable cofactor of anorectal symptoms.

Rheumatoid Arthritis

GI manifestations of rheumatoid arthritis (RA) are varied and often catastrophic. The spectrum of GI involvement includes oropharyngeal dysphagia, esophageal dysphagia, mesenteric vasculitis, amyloidosis, and Felty syndrome.

Severe sicca manifestations from associated Sjögren syndrome may interfere with deglutition and cause oropharyngeal dysphagia in RA. Abnormal esophageal motility, with low-amplitude peristaltic contractions and reduced lower esophageal sphincter pressures, predisposes patients with RA to reflux, dysphagia, and esophagitis.

Rheumatoid vasculitis of the GI tract is rare but often catastrophic. Presentations vary with involvement of small arterioles causing ischemic ulcers and perforation, while large-vessel vasculitis results in extensive bowel infarction and intraperitoneal hemorrhage. Patients with rheumatoid mesenteric vasculitis may present with appendicitis, cholecystitis, or bowel obstruction from stricture formation.

RA is the most common disease causing AA amyloidosis. Long-standing RA with poorly controlled inflammation is the major risk factor for development of AA amyloidosis. GI tract involvement is common with AA amyloidosis (see Amyloidosis subsection above). RA also is associated with liver disease, including mild liver function test abnormalities, autoimmune hepatitis, and primary biliary cirrhosis. RA may be part of Felty syndrome (splenomegaly and neutropenia) with nodular regenerative hyperplasia and portal hypertension (variceal hemorrhage).

Systemic Lupus Erythematosus

SLE is a multisystem disease that predominantly affects women and can involve the entire GI tract and liver. Approximately 15% of SLE patients have skeletal myopathy that affects the upper one-third of the esophagus and results in hoarseness and dysphagia from involvement of laryngeal and pharyngeal muscles. Patients with esophageal dysmotility may have heartburn, regurgitation, and dysphagia. Mesenteric vasculitis can involve the stomach, small intestine, and colon. The presentation of patients with intestinal vasculitis ranges from nausea, vomiting, and abdominal pain to an acute abdomen. Mesenteric vasculitis is almost always accompanied by lupus involvement of other organ systems. Less common GI complications of SLE that may be the initial manifestation of lupus include intestinal pseudo-obstruction and protein-losing enteropathy. Primary lupus peritonitis is rare and sometimes occurs without ascites. Patients with primary lupus peritonitis present with abdominal pain simulating an acute abdomen, typically during a lupus flare. It responds to corticosteroids. Hepatic involvement in SLE includes mildly abnormal liver enzyme levels, fatty liver, nodular regenerative hyperplasia, autoimmune hepatitis, and primary biliary cirrhosis.

Vasculitides

Systemic vasculitides involve the GI tract to a variable degree. Symptoms and signs of systemic vasculitis involving the GI tract result from mesenteric ischemia. The vasculitides with well-described and frequent GI involvement include Behçet disease (BD), polyarteritis nodosa (PAN), and Henoch-Schönlein purpura (HSP).

Behçet Disease

BD is a vasculitis that may involve blood vessels of all sizes and both arterial and venous circulations. Recurrent oral ulceration is the sine qua non of BD. It typically affects individuals in the second through fourth decades of life. Its prevalence is similar in men and women, with more severe disease in men. GI involvement is variable. The small intestine and colon are the most frequently involved segments of the GI tract. Intestinal involvement may occur either from small-vessel disease with mucosal ulceration or from large-vessel disease resulting in ischemia and infarction. Intestinal lesions occur most frequently in the ileocecal region with the characteristic endoscopic finding of deep, punched-out ulcers. Complications include intestinal perforation from penetrating ulcers and type AA amyloidosis, with diarrhea and malabsorption.

BD with GI involvement may be difficult to distinguish from Crohn disease since oral and genital ulcers and rectal sparing occur in both conditions. In addition, the 2 diseases share extraintestinal manifestations, such as uveitis, skin changes, and arthritis. However, a small-vessel vasculitis with deep ulcerations, no cobblestoning, and absence of granulomas characterizes BD. Large-vessel involvement may cause Budd-Chiari syndrome or portal vein thrombosis. BD has an unpredictable course, with immunosuppressive medications being the mainstay of treatment.

Polyarteritis Nodosa

PAN is a necrotizing vasculitis of medium-sized arteries that involves many different organ systems. It is associated with hepatitis B virus infection in about 7% of cases, but PAN develops in less than 1% of patients with hepatitis B. Patients with PAN have a variable clinical presentation; up to 65% of patients have GI involvement. The small intestine is the most commonly affected part of the GI tract, followed by the mesentery and colon. The most frequent symptom is postprandial abdominal pain from intestinal ischemia. Ischemia limited to the intestinal mucosa results in ulceration and GI bleeding. Bowel perforation may occur from transmural ischemic necrosis. Acalculous ischemic cholecystitis may develop from arteritis involving the wall of the gallbladder. Liver involvement may manifest as liver infarction, acute liver failure, nodular regenerative hyperplasia, and hemobilia from

hepatic artery aneurysm rupture. Angiography, the main method of diagnosing PAN, typically shows saccular aneurysms. Tissue biopsy confirms the diagnosis—a common biopsy site is the sural nerve. Corticosteroids are the mainstay of treatment.

Henoch-Schönlein Purpura

HSP is a systemic, small-vessel, leukocytoclastic vasculitis characterized by the tetrad of palpable purpura, arthralgias, renal disease, and GI involvement. It is the most common systemic vasculitis of children; however, it can occur in adults. The cutaneous hallmark of HSP is palpable purpura of dependent areas such as the legs and arms (Figure 13.9). In palpable purpura, blood leaks from injured vessels into the tissues. GI involvement in adult-onset HSP is common, with GI symptoms caused by immune complex deposition in vessel walls, which leads to impaired perfusion and ischemia. The most common GI features are abdominal pain and bleeding. The abdominal pain is characteristically located in the periumbilical area and, as in chronic mesenteric ischemia, the pain worsens after meals. The small intestine is the most frequently involved site in the GI tract. Computed tomography characteristically shows small-bowel wall thickening involving mainly the jejunum and ileum. Complications include intussusception, perforation, and stricture.

The diagnosis is made by the presence of palpable purpura along with 1 of the following: abdominal pain, IgA deposition, arthritis, or renal involvement. HSP can be difficult to diagnose, especially if the GI symptoms develop before the characteristic cutaneous lesions, as in 15% of cases. In addition, when the ileum is involved, the presentation and findings mimic Crohn disease. GI manifestations of HSP typically resolve without treatment. The role of corticosteroids to prevent complications and relapses is controversial. Adults may have malignancies associated with HSP, with solid tumors being the most common (non–small cell lung carcinoma and prostate cancer). Appropriate cancer screening and surveillance among adults with a new diagnosis of HSP is important.

Gynecologic Conditions

Endometriosis can affect the gut; most frequently, the sigmoid colon is involved. It can cause obstruction (adhesions), perforation, bleeding, diarrhea, and, more often, abdominal pain or constipation. These GI tract symptoms may or may not be cyclical. Associated gynecologic symptoms, such as pain with intercourse, are common. Estrogen administration after menopause may be associated with symptoms. Patients with Meigs syndrome present with ascites and, often, pleural effusion in association with benign ovarian neoplasms.

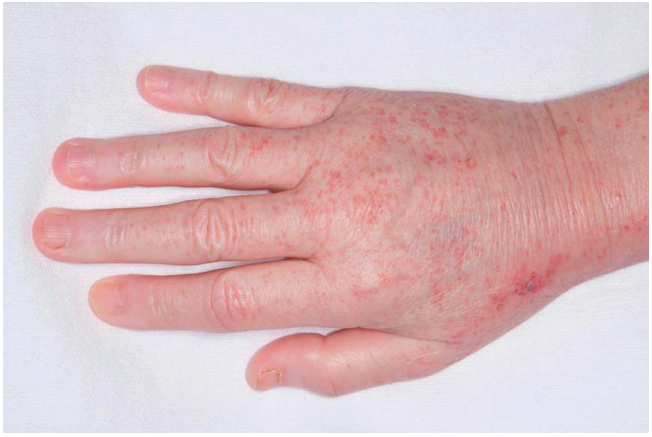

Figure 13.9. Henoch-Schönlein Purpura. These discrete hemorrhagic papules were on the hand of a patient with Henoch-Schönlein purpura.

Miscellaneous Conditions

The vascular type (type IV) of Ehlers-Danlos syndrome, usually autosomal dominant, is associated often with bowel perforation, vascular aneurysms, arteriovenous fistulas, and rupture.

Paraneoplastic syndromes with diffuse GI tract motor dysfunction occur most often with small cell lung carcinoma, often with autonomic neuropathy, cerebellar degeneration, peripheral neuropathy, seizures, or syndrome of inappropriate secretion of antidiuretic hormone. Type 1 antineuronal nuclear antibodies usually are detectable.

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Questions and Answers

Questions

Abbreviations used:

ALT,	alanine aminotransferase
CBC,	complete blood cell count
CIPO,	chronic intestinal pseudo-obstruction
CMV,	cytomegalovirus
CT,	computed tomographic
EGD,	esophagogastroduodenoscopy
ELP,	esophageal lichen planus
ERCP,	endoscopic retrograde cholangiopancreatography
GI,	gastrointestinal
HHT,	hereditary hemorrhagic telangiectasia
HIV,	human immunodeficiency virus
HSV,	herpes simplex virus
INR,	international normalized ratio
IV,	intravenous
KTW,	Klippel-Trénaunay-Weber
LDH,	lactate dehydrogenase
NSAID,	nonsteroidal antiinflammatory drug
PPI,	proton pump inhibitor
SIBO,	small intestinal bacterial overgrowth

Multiple Choice (choose the best answer)

IV.1. **A 25-year-old man with a long history of IV drug abuse and little medical care presents with fever, 12-kg weight loss, diarrhea, and anemia. He has diffuse abdominal tenderness on examination. Laboratory test results show mild pancytopenia, hypokalemia, decreased serum albumin, and increased ALT and LDH. An HIV test is positive with a CD4 cell count of 45/μL. An abdominal-pelvic CT scan with oral and IV contrast media shows bulky, enlarged mesenteric lymph nodes and slight hepatosplenomegaly. The pancreas is normal. A colonoscopy is unremarkable, but patchy areas of edema, erythema, and nodularity with frosted yellowish plaques are found in the duodenum. Which of the following is the most likely diagnosis?**

a. Histoplasmosis
b. Infection with *Mycobacterium avium-intracellulare* complex
c. Infection with *Cryptosporidium*
d. Non-Hodgkin lymphoma, T-cell lineage
e. Kaposi sarcoma

IV.2. **A 39-year-old woman recently received a diagnosis of HIV infection after presenting with *Candida* esophagitis, which was treated with fluconazole. One week after completing this therapy, she is about to start HIV therapy, but diarrhea develops with bright red blood, diffuse abdominal discomfort, and fevers. No one else around her is sick, and she has not been around animals or children. There is no travel history. On examination, she looks chronically ill and is uncomfortable. Which of the following is most likely to be found at colonoscopy?**

a. Patchy sigmoid ulcerations, and biopsies showing intranuclear inclusions, perinuclear halo, and cytoplasmic inclusions
b. Patchy sigmoid ulcerations, and biopsies showing ground-glass nuclei, eosinophilic intranuclear inclusions, and multinucleate cells
c. Terminal ileum edema, and biopsies showing mild villous atrophy with apical intracellular, extracytoplasmic inclusions
d. Numerous focal vascular lesions, and biopsies showing angioproliferative lesions with adjacent spindle cells, positive for human herpesvirus 8 latent antigen
e. Normal colonoscopy and positive stool testing for *Clostridium difficile*

IV.3. **A 32-year-old man with HIV infection is hospitalized for acute pancreatitis. He does not drink alcohol, and his gallbladder was removed 5 years ago. He has never had pancreatitis before. His medications include didanosine, trimethoprim-sulfamethoxazole, pentamidine, fluconazole,**

and furosemide. Which of these medications would be safe to continue?

a. Didanosine
b. Trimethoprim-sulfamethoxazole
c. Pentamidine
d. Fluconazole
e. Furosemide

IV.4. A 34-year-old man with HIV infection presents with a history of 12 weeks of diarrhea. He reports no fever or chills but has lost 1.8 kg of weight. He has not had nausea, vomiting, abdominal pain, or blood in his loose-to-watery brown stools. He has not adhered to his medical therapy and has not taken antibiotics in months. There is no travel or exposure history. Stool testing for enteric pathogens, Shiga toxin, fecal leukocytes, *Clostridium difficile*, ova and parasites, and occult blood are negative. Which of the following is most likely?

a. Enterohemorrhagic *Escherichia coli*
b. Enteroinvasive *E coli*
c. Enterotoxigenic *E coli*
d. Enteropathogenic *E coli*
e. Enteroadherent *E coli*

IV.5. A 59-year-old woman complains of 3 episodes of food sticking in the lower chest. Each time, it has been solid food, such as roast beef. After 30 seconds, it passes. She has a history of infection with HIV and has adhered to her medical therapy for several years, with a normal CD4 cell count. In the past year she has been having mild attacks of asthma, usually occurring after she goes to bed. Her physician prescribed a corticosteroid inhaler last month. Two weeks ago, thrush was diagnosed, and she began treatment with fluconazole. One day ago, she had another episode of mild dysphagia. She denies having fever, chills, sweats, weight loss, or diarrhea. She avoids use of NSAIDs, tobacco, alcohol, fatty foods, chocolate, mint, coffee, and citrus. Which of the following is most likely to be found at endoscopy?

a. A cluster of focal ulcerations in the midesophagus
b. Los Angeles grade C esophagitis
c. *Candida* esophagitis
d. CMV esophagitis
e. Diffuse circular rings and linear furrows

IV.6. A 27-year-old man was found to be HIV-infected 1 year ago, and although he has not been adherent to his medical therapy, he has been careful to avoid exposure to infectious agents. He avoids travel, animals, and young children. When invited to a friend's house for a New England lobster feast, he helped with food preparation but did not consume any raw oysters or clams. A few hours after the party, he noted a painful swollen area surrounding a cut on his right hand, which became larger and increasingly painful over a 2-hour period. Which of the following is the most likely cause of this?

a. *Vibrio parahaemolyticus*
b. *Vibrio cholerae*
c. *Vibrio vulnificus*
d. *Vibrio mimicus*
e. *Vibrio fluvialis*

IV.7. A 52-year-old man who receives warfarin for recent deep vein thrombosis has an INR of 2.3 and presents with hematemesis and orthostasis. His INR is corrected with fresh frozen plasma to 1.2. He undergoes EGD after volume resuscitation within 8 hours of his original presentation. A 2-cm gastric ulcer was seen with a nonbleeding, 1-mm, visible vessel on the greater curvature of the stomach in the antrum and was treated with epinephrine injection and heater-probe therapy. The patient was given IV continuous infusion PPI therapy. The patient's hemoglobin values are shown.

Day	*Hemoglobin, g/dL*	*INR*
Admission	**13.2**	**2.3**
1	**9.2**	**1.6**
2	**8.4**	**2.0**
3	**7.6**	**1.9**

On day 2 he passes 2 formed, black stools, and on day 3, he passes 1 black, formed stool. His vital signs are stable. On day 3, which treatment would be appropriate?

a. Advance the diet and observe
b. Repeat the EGD
c. Infuse 2 more units of fresh frozen plasma
d. Infuse 2 more units of fresh frozen plasma and repeat the EGD
e. Add sucralfate to his medical treatment

IV.8. A 72-year-old woman has 2 episodes of red hematemesis associated with orthostasis over a 5-day period. She has 3 alcoholic drinks daily and uses ibuprofen daily. She undergoes 2 EGDs with normal results; both are done about 5 hours after each episode. What is the most likely diagnosis?

a. Gastric varices
b. Gastric Dieulafoy lesion
c. Gastric vascular ectasia
d. NSAID gastric ulcer
e. Duodenal ulcer

IV.9. A 62-year-old man with diabetes mellitus and chronic obstructive pulmonary disease has upper GI tract bleeding that requires 2 units of packed red blood cells transfused for a 1-cm posterior duodenal bulb ulcer that did not require endoscopic therapy. His rapid urease test on gastric biopsy was negative, and *Helicobacter pylori* serology was negative. He takes no NSAIDs (including aspirin) and does not smoke. You see him in the clinic 5 days after discharge. What would be the most appropriate treatment?

a. PPI twice daily for 8 weeks
b. PPI once daily for life
c. PPI once daily for 4 weeks
d. PPI once daily for 4 weeks, with amoxicillin 1 g twice daily and clarithromycin 1 g twice daily for 2 weeks
e. PPI twice daily, with bismuth subsalicylate 2 tablets 4 times daily, tetracycline 500 mg 4 times daily, and metronidazole 500 mg 4 times daily for 2 weeks, followed by PPI once daily for 4 more weeks

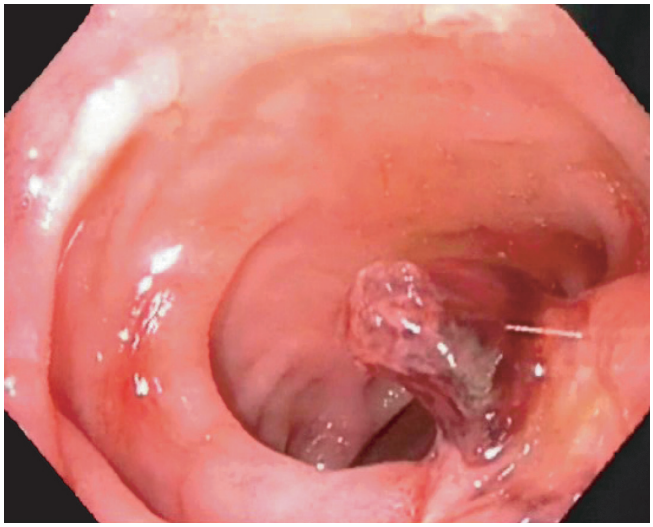
IV.10. A 28-year-old woman presents with necrotizing gallstone pancreatitis. She undergoes endoscopic sphincterotomy and stone extraction on day 2. Several extrapancreatic and one 8-cm intrapancreatic fluid collections are seen on CT on day 10. On day 13, hematochezia and orthostasis develop, and she receives 4 units of packed red blood cells. An upper endoscopy shows a maroon clot in the distal duodenum without evidence of active bleeding. The clot was washed, showing no evident underlying pathology and no active bleeding. The ampulla seen with the side-viewing scope shows only a sphincterotomy site. The patient is hemodynamically stable for 12 hours, and then tachycardia and hematochezia redevelop. Which therapeutic option would likely be most successful?

a. EGD and epinephrine injection at the sphincterotomy site
b. Diagnostic laparotomy
c. Angiographic embolization
d. Octreotide infusion
e. Continuous infusion of PPI

IV.11. **A 65-year-old woman presents with hematochezia. She had 2 large-volume mushy, bloody stools followed by 3 passages of frank blood over the past 5 hours, the last of which was associated with a brief syncopal episode. She has been taking antibiotics for an upper respiratory infection for the past week. She has had no recent diarrhea and has no abdominal pain. Upon arrival in the emergency department, her blood pressure is 125/80 mm Hg, and her pulse is 92 beats per minute; on standing, her systolic blood pressure decreases by 20 mm Hg and her pulse increases by 12 beats per minute. Her hemoglobin level is 12.8 g/dL. What is the most likely cause of bleeding?**

a. Diverticular bleeding
b. *Clostridium difficile* colitis
c. Duodenal ulcer
d. Ischemic colitis
e. Gastric Dieulafoy lesion

IV.12. **A 43-year-old man presents with a history of having 3 melenotic, soft stools over a 12-hour period. He has no abdominal pain and uses no NSAIDs (including aspirin). His blood pressure is 98/60 mm Hg and his pulse is 108 beats per minute with significant orthostatic change. His hemoglobin level is 10.0 g/dL with a normal mean corpuscular volume. He is receiving a continuous infusion of a PPI. The EGD image shows the finding in the posterior duodenal bulb after vigorous lavage, without any evidence of active bleeding. Which is a true statement about this clinical scenario?**



a. Both clot removal with endoscopic therapy and PPI infusion therapy alone are acceptable options
b. The chance of rebleeding is more than 50% for this patient
c. This is the most likely location of an aortoenteric fistula
d. This lesion is most likely associated with the left gastric artery
e. This lesion is often malignant

IV.13. **A 45-year-old woman, previously in good health except for migraine headaches, has constant left lower quadrant discomfort with an urge to have a bowel movement. Shortly thereafter, she passes a loose brown stool followed by several small loose stools mixed with blood. She does not have fever or chills, and no one around her has been ill. She denies travel, recent antibiotics, and exposure to animals or children, and she does not smoke tobacco or drink alcohol. Her only medication is a triptan that she takes for migraine about twice a week. On admission, she has moderate pain upon palpation of her left lower quadrant and is mildly tachycardic with a regular pulse. In the emergency department, an abdominal-pelvic CT scan with oral and IV contrast media shows a segmental area of edema involving the sigmoid colon with multiple sigmoid diverticula. Colonoscopy shows a well-demarcated area of ulceration, edema, and erythema in the sigmoid colon with diverticula throughout the sigmoid colon. Which of the following is the most likely diagnosis?**

a. Diverticular disease–associated segmental colitis
b. Crohn disease
c. *Clostridium difficile* infection
d. Shigellosis
e. Ischemic colitis

IV.14. **A 26-year-old woman presents to the emergency department after having several days of loose stools, now with streaks of bright red blood, and intermittent left lower quadrant pain. She denies fever, chills, and exposure to sick persons, animals, or children, and she has not traveled or recently taken antibiotics. She does not smoke tobacco or drink alcohol, and she has no significant medical or surgical history. Results of her laboratory tests (CBC, creatinine, liver function tests, serum albumin, urinalysis, pregnancy test, and C-reactive protein) are all normal or negative. On physical examination, she has mild tenderness over her sigmoid colon in the left lower quadrant. A CT scan with oral and IV contrast media shows old thrombotic occlusion of the inferior vena cava with recanalization and multiple collaterals, an edematous segment of sigmoid colon, and thrombus within the inferior mesenteric vein. Which of the following best explains these findings?**

a. Crohn disease
b. Prothrombin gene mutation
c. Cirrhosis
d. Factor V Leiden gene mutation
e. Diverticulitis

IV.15. **A 59-year-old woman presents to the emergency department because she had acute periumbilical pain for 3 hours. For the past 2 months, she has felt "nervous" and has had 2 or 3 loose stools daily. She has lost 3.6 kg of body weight over this period despite having a good appetite. Her only medical or surgical history is a previous cholecystectomy, and she does not smoke tobacco or drink alcohol. She is afebrile. Her blood pressure is 139/95 mm Hg, with an irregular pulse at 125 beats per minute. On physical examination, she has an enlarged, tender thyroid as well as vague, mild periumbilical tenderness. An abdominal-pelvic CT scan with oral and IV contrast media is unremarkable. Her CBC, creatinine, and liver function tests show a white blood cell count of 13,400/μL. Which of the following is the most likely cause of her acute symptoms?**

a. Celiac disease
b. Acute appendicitis
c. Superior mesenteric artery embolus
d. Carcinoid syndrome
e. Hyperthyroidism

IV.16. **A 72-year-old man is admitted to the hospital with acute cholecystitis. He has a history of coronary artery disease (he takes aspirin and a β-blocker), tobacco use, mild hypertension, and type 2 diabetes mellitus (he takes insulin). His white blood cell count is elevated (16,200/μL), and creatinine is 1.7 mg/dL, with normal liver function test and serum lipase results. Ultrasonography of the abdomen is consistent with acute cholecystitis with cholelithiasis. After an unremarkable cholecystectomy, he has nausea, vague but mild abdominal discomfort, and abdominal distention, which improve with nasogastric suction. However, over several days he cannot be weaned from the nasogastric tube. His blood pressure is 107/78 mm Hg, his pulse rate is 68 beats per minute and regular, he is afebrile, and his liver function test and lipase results remain normal, with a creatinine of 1.9 mg/dL and a normal white blood cell count. A plain radiograph of the abdomen shows mild, nonspecific dilatation of a few small bowel loops**

with increased gas and fluid but no transition point. Which of the following would you recommend next?

a. ERCP
b. Abdominal-pelvic CT scan with oral and IV contrast media
c. CT angiography
d. CT enterography
e. Doppler ultrasonography of the abdominal (visceral) arteries

IV.17. A 26-year-old previously healthy woman, gravida 3 parity 2, at week 16 of her pregnancy presents with an acute episode of left upper quadrant pain with radiation to her left shoulder and nausea, lasting 2 hours, that is now resolved. She has never had this pain before and denies any history of heartburn, ulcers, and hepatobiliary or pancreatic disease. She has never had surgery and does not smoke tobacco or drink alcohol. Her physical examination and laboratory test results are unremarkable. A CT scan shows a 1.9-cm splenic artery aneurysm. Which of the following would you recommend?

a. Observe
b. Reevaluate with ultrasonography in 3 months
c. Reevaluate with CT scan in 6 months
d. Consult with an interventional radiologist for therapy
e. Consult with a surgeon for splenectomy

IV.18. A 59-year-old man who was previously well is seen for recurrent abdominal pain that has been going on for several weeks. The pain occurs only after meals, usually about 30 minutes after eating. It is dull, achy, and periumbilical, and it lasts about an hour. It is getting worse. He has lost 4.5 kg of body weight over 2 months. Fevers, fatigue, arthralgias, and new hypertension also have recently developed. On physical examination, there is livedo reticularis of the lower extremities with mild edema. Laboratory tests show an elevated erythrocyte sedimentation rate (105 mm/1 h); normal liver function tests, creatine kinase, and CBC; elevated serum creatinine; and negative testing for HIV, hepatitis B virus, antinuclear antibody, and antineutrophil cytoplasmic autoantibody. Which of the following would be the best next diagnostic test?

a. Sural nerve biopsy
b. Renal biopsy
c. Small-bowel biopsy
d. Mesenteric angiography
e. Muscle biopsy

IV.19. A 45-year-old woman with HHT presents for follow-up evaluation of iron deficiency anemia. She takes oral iron supplementation. She denies melena or hematochezia. She reports progressive fatigue. In addition, she has dyspnea on exertion and reports sleeping on 2 pillows with occasional nocturnal awakenings for shortness of breath over the past 2 months. On physical examination, she has mild tachycardia, jugular venous distention to the angle of the jaw, and a systolic flow murmur on cardiac auscultation. She has mild bilateral pitting edema of the lower extremities. Laboratory test results include hemoglobin 12.5 g/dL and mildly elevated serum urea nitrogen (25 mg/dL) and creatinine (1.2 mg/dL). Which pathophysiologic abnormality most likely accounts for this patient's symptom complex?

a. Portal vein–hepatic vein fistula
b. Hepatic artery–hepatic vein fistula
c. Hepatic artery–portal vein fistula
d. Nodular regenerative hyperplasia
e. Hepatic vein thrombosis

IV.20. A 23-year-old man presents with intermittent episodes of painless hematochezia requiring blood transfusions. He denies recurrent epistaxis or melena. There is no family history of GI bleeding. His vital signs are stable. Physical examination shows conjunctival pallor, his left leg is significantly larger than the right, his left thigh has large cutaneous hemangiomas, and both lower extremities have venous varicosities. Laboratory test results include hemoglobin 8 g/dL and platelet count $300\times10^3/\mu L$. From the history, clinical presentation, and physical examination findings, what is the most likely cause of the recurrent hematochezia?

a. Diverticulosis
b. Internal hemorrhoids
c. Rectal hemangioma
d. Rectal varicies
e. Dieulafoy lesion

IV.21. A 25-year-old woman presents with severe, diffuse abdominal pain of 12 hours' duration associated with nausea and constipation. She reports similar episodes of abdominal pain over the past 5 years, and she recently received a diagnosis of acute intermittent porphyria. Physical examination findings include blood pressure 170/110 mm Hg, heart rate 115 beats per minute, and tachypnea. Which of the following is the definitive treatment of an acute porphyric attack?

a. IV hemin
b. IV glucose
c. Promethazine
d. Ondansetron
e. IV albumin

IV.22. A 40-year-old woman with scleroderma presents for evaluation of recurrent episodes of nausea, vomiting, and abdominal pain. On physical examination, she has a distended, tympanitic abdomen with diminished bowel sounds. She reports that during the episodes, she has abdominal bloating and frequent, loose, watery stools. CT enterography shows dilatation of the entire small bowel without mechanical obstruction. What is the best next step in the management of her recurrent symptoms?

a. Segmental intestinal resection
b. Intestinal transplant
c. Ciprofloxacin
d. Octreotide 200 mcg subcutaneously every evening
e. Total parenteral nutrition

IV.23. A 62-year-old woman presents with substernal burning discomfort along with progressive, intermittent, solid food dysphagia for 1 year. Symptoms have not improved with a 6-month course of acid-suppressive therapy. She has no history of smoking, drinking alcohol, or having long-standing reflux, weight loss, or anorexia. A barium esophagram shows a small-caliber esophagus. Upper endoscopy shows esophageal luminal narrowing with multiple mucosal rings. Esophageal biopsies show a dense subepithelial lymphocytic infiltrate, intraepithelial lymphocytes, and multiple eosinophilic necrotic keratinocytes. What is the most likely diagnosis?

a. Gastroesophageal reflux disease
b. Eosinophilic esophagitis
c. Lichen planus
d. Epidermolysis bullosa
e. Esophageal Crohn disease

IV.24. In a patient with suspected GI amyloidosis, what is the most common site of gut involvement?

a. Esophagus
b. Stomach
c. Duodenum
d. Jejunum
e. Colon

Answers

IV.1. Answer b.
This very immunosuppressed man with HIV infection, fever, weight loss, and severe diarrhea most likely has an infiltrating malignancy or infection, probably affecting multiple organs, including mesenteric lymph nodes and the small bowel. *Mycobacterium avium-intracellulare* complex typically involves the small bowel and mesenteric lymph nodes, and the endoscopic findings are highly suggestive. Non-Hodgkin lymphoma would usually be of B-cell lineage; non-Hodgkin lymphoma of T-cell lineage would be more typical of celiac disease. While *Cryptosporidium* could cause diarrhea, malabsorption, and weight loss, the lymph node involvement would be unusual. Kaposi sarcoma would have a different endoscopic appearance.

IV.2. Answer a.
This chronically ill, immunosuppressed woman with HIV has bloody diarrhea with fever and abdominal pain. An enteric bacterial pathogen is likely, but the answer choices include CMV (*a*), HSV (*b*), *Cryptosporidium* (*c*), Kaposi sarcoma (*d*), and *Clostridium difficile* (*e*). CMV colitis (choice *a*) is the best answer, with endothelial inclusions (base of ulcer) as described. HSV would be unusual in the colon, *Cryptosporidium* would not cause bloody diarrhea, and Kaposi sarcoma usually is asymptomatic and does not cause diarrhea. Infection from *C difficile*, which could occur after use of fluconazole, usually does not cause bloody diarrhea, and the colonoscopy in that case would not likely be normal.

IV.3. Answer d.
Medications frequently implicated in pancreatitis in HIV-infected patients include didanosine, pentamidine, dapsone, trimethoprim-sulfamethoxazole, furosemide, metronidazole, and nelfinavir. Fluconazole would not likely cause this patient's acute pancreatitis.

IV.4. Answer e.
HIV-infected persons are at risk for infections with enteroadherent *Escherichia coli*, which causes chronic diarrhea. This organism can also cause acute diarrhea both in travelers and in children who are not immunosuppressed. Treatment with ciprofloxacin may be beneficial. Enterohemorrhagic and enteroinvasive *E coli* infections often are diagnosed by stool culture or testing for Shiga toxin and often are accompanied by fecal leukocytes, bleeding, or occult blood. Enterotoxigenic *E coli* is more common in travelers, and enteropathogenic *E coli* is more common in children, especially those younger than 6 months.

IV.5. Answer b.
Statistically, this nonimmunosuppressed HIV-infected patient (with years of adherence to her medical therapy) with a few episodes of dysphagia, avoidance of tobacco, alcohol, fatty foods, chocolate, mint, coffee, and citrus, most likely has gastroesophageal reflux disease with esophagitis (answer choice *b*). Her thrush, likely due to her corticosteroid inhaler, has been treated for 2 weeks with fluconazole. Thus, *Candida* esophagitis is unlikely. Pill esophagitis (answer choice *a*; she has no odynophagia, and her dysphagia is in the lower chest not the middle chest) and CMV esophagitis (answer choice *d*; she has no odynophagia and is not immunosuppressed) are unlikely. Eosinophilic esophagitis (answer choice *e*) is unlikely given her sex and age.

IV.6. Answer c.
Vibrio mimicus, Vibrio fluvialis, and *Vibrio parahaemolyticus* are much more likely to cause a diarrhea syndrome than a wound infection. *Vibrio cholerae* infection typically results in diarrhea. *Vibrio vulnificus* more often results in rapidly progressive wound infections, especially in immunosuppressed patients, and in patients with iron-storage disease or cirrhosis. Hand injuries from the preparation of raw shellfish or fish allow this organism to invade soft tissues, resulting in rapid, progressive, life-threatening cellulitis, myositis, or fasciitis.

IV.7. Answer a.
The slow decrease in the hemoglobin level is consistent with reequilibration. There is no evidence of clinical bleeding and the 1 formed, black stool is consistent with recent bleeding. No specific treatment is needed.

IV.8. Answer b.
All these are possible explanations, but the Dieulafoy lesion is the best answer. Gastric varices and the NSAID ulcer would likely be seen at endoscopy. The vascular ectasia could be a difficult lesion to visualize, but the red hematemesis and orthostasis are consistent with arterial bleeding, as seen with a Dieulafoy lesion. The majority of these are in the upper stomach.

IV.9. Answer b.
Most duodenal ulcers heal in 4 weeks with once-daily PPI therapy. A patient may have a false-negative rapid urease test with upper GI tract bleeding, but the *Helicobacter pylori* serology, although not completely sensitive, should remain positive. Anti–*H pylori* therapy might still be supportable but is not the best answer. Patients with peptic ulcer disease bleeding without a correctable cause have a recurrent bleeding rate of about 30% at 5 years. Patients without a correctable etiologic factor for peptic ulcer disease (*H pylori*, NSAIDs), especially those with comorbidities, should receive long-term PPI or full-dose histamine$_2$-blocker therapy for prophylaxis.

IV.10. Answer c.
The most likely source of the major bleeding is a pseudoaneurysm secondary to the necrotic pancreatitis. This is difficult to operate on in the face of acute pancreatic necrosis. The best treatment is angiographic embolization. Bleeding from the sphincterotomy site is possible, but treatment at that site is not the best answer. This possibility would be less likely with the normal appearance of the sphincterotomy site and the fact that the procedure was performed more than 10 days before the clinical bleeding. Octreotide might be a temporizing measure in the face of exsanguinating bleeding, but it is not the best answer.

IV.11. Answer a.
These findings are most consistent with diverticular bleeding. The stool is large volume and the abdomen is painless. The normal hemoglobin and minor orthostatic change associated with the multiple red stools are consistent with a colonic source of bleeding. Vagal-induced syncope can be seen with colonic bleeding. The degree of blood loss is atypical for *Clostridium difficile* colitis, and patients with ischemic colitis generally present with abdominal pain.

IV.12. Answer a.
This is an adherent clot over a benign duodenal bulb ulcer in a patient not actively bleeding. Both aggressive clot removal with endoscopic therapy and IV PPI treatment alone are acceptable

management options. The chance of rebleeding with an adherent clot is about 25%. Aortoenteric fistulas are most commonly associated with the distal third of the duodenum. The posterior bulb ulcer is usually associated with the posterior gastroduodenal artery distribution. The left gastric artery is usually associated with the lesser curve of the stomach.

IV.13. Answer e.
The clinical history and colonoscopic findings are most consistent with ischemic colitis, possibly secondary to the patient's use of triptan. The CT scan did not show diverticulitis, and diverticular disease–associated segmental colitis is an uncommon chronic illness with features more reminiscent of chronic colitis. A patient with shigellosis or Crohn disease could present with segmental colitis, but shigellosis is uncommon and this would be an unusual acute clinical presentation for a patient with Crohn disease. The colonoscopic findings would not be typical of *Clostridium difficile* colitis.

IV.14. Answer d.
This patient presents with acute thrombosis of the inferior mesenteric vein, which could occur with any of these conditions. However, she also has chronic vascular thrombosis with occlusion of her inferior vena cava, which is much more likely to occur with the G1691 factor V (Leiden) gene mutation than with the G20210A factor II (prothrombin) gene mutation. Her CT and clinical history do not support the other diagnoses (Crohn disease, cirrhosis, or diverticulitis).

IV.15. Answer c.
This woman has hyperthyroidism (tender thyroid, nervousness, loose stools, and weight loss) with atrial fibrillation (irregular pulse) and new periumbilical pain without much tenderness on examination, which is consistent with acute mesenteric ischemia that most likely resulted from embolism in the superior mesenteric artery. Celiac disease is associated with other autoimmune disorders, especially of the thyroid, but would not explain her acute symptoms. Acute appendicitis usually does not start with acute abdominal pain and an elevated white blood cell count. Anorexia and nausea would be more typical early symptoms. Carcinoid syndrome could account for her 2-month history of loose stools, but acute abdominal pain would be unlikely in the absence of small-bowel obstruction. Hyperthyroidism alone does not account for all her symptoms.

IV.16. Answer e.
This patient most likely has a small-bowel ileus. Given his medical history, small-bowel vascular disease needs to be considered. There is nothing to suggest sepsis, hypotension, or a low-flow state with nonocclusive mesenteric ischemia. Small-bowel obstruction, pancreatitis, cholangitis, or a biliary complication from his recent surgery seem unlikely; thus, an ERCP is not indicated. Mesenteric ischemia should be a consideration. Because of his elevated creatinine, the use of IV contrast media (answer choices *b, c*, and *d*) would best be avoided. Doppler ultrasonography of his celiac artery, superior mesenteric artery, and inferior mesenteric artery would be safe, and the presence of significant proximal arterial occlusions in this patient with multiple risk factors for chronic mesenteric atherosclerotic arterial disease would increase the suspicion of acute-on-chronic mesenteric arterial thrombosis, with subsequent angiography, angioplasty, or surgery. The absence of significant proximal arterial lesions would prompt reevaluation of alternative nonvascular disorders.

IV.17. Answer d.
Splenic artery aneurysms, if asymptomatic and 2 cm or greater in diameter, require therapy (with interventional radiology or surgery). Symptomatic splenic artery aneurysms or those discovered during pregnancy (high risk for bleeding) should also be treated. In this case, treatment by interventional radiology would be preferable to a major operation (splenectomy).

IV.18. Answer d.
This patient most likely has polyarteritis nodosa. Without neuromuscular symptoms, sural nerve biopsy and muscle biopsy are less likely to be diagnostic, in contrast to visceral angiography, which should demonstrate microaneurysms involving the branch points of medium-sized arteries. Mucosal biopsies of the GI tract are not likely to be diagnostic. Renal biopsy may be diagnostic, but it carries a greater risk.

IV.19. Answer b.
This patient presents with symptoms and signs of heart failure. HHT can involve the liver with vascular malformations of various sizes. With the dual blood supply to the liver, 3 different types of abnormal vascular communications may form: portal vein–hepatic vein (portovenous) fistula, hepatic artery–hepatic vein (arteriovenous) fistula, and hepatic artery–portal vein (arterioportal) fistula. These 3 hepatic vascular malformations likely occur concomitantly, but usually 1 of them predominates functionally and clinically. The 3 most common and distinct clinical manifestations that result from liver vascular malformations in HHT are high-output cardiac failure, biliary ischemia, and portal hypertension. High-output cardiac failure is the most common and results from chronic shunting of blood from the hepatic artery to the hepatic vein (answer choice *b*). The definitive way to establish the diagnosis of hepatic vascular involvement is with an imaging study, such as a CT scan. CT imaging typically shows simultaneous visualization of the arterial and hepatic venous phases in the arterial phase, which is highly suggestive of a hepatic artery–hepatic vein fistula. Nodular regenerative hyperplasia is characterized by the presence of regenerative nodules that compress the surrounding liver parenchyma, resulting in portal hypertension. These nodules, unlike those in true cirrhosis, are not delimited by fibrous septa. HHT is associated with the development of nodular regenerative hyperplasia of the liver, but nodular regenerative hyperplasia and hepatic vein thrombosis would not manifest with symptoms of heart failure.

IV.20. Answer c.
This is a case of KTW syndrome, which is a congenital vascular disorder characterized by the triad of limb hypertrophy, cutaneous hemangiomas, and varicosities. Transfusion-dependent anemia and life-threatening GI bleeding may result from cavernous hemangiomas of the rectum, which is the most common reported cause of GI bleeding in KTW syndrome (answer choice *c*). Other potential causes of GI hemorrhage related to KTW syndrome include localized rectal varices caused by an obstructed internal iliac system or portal hypertension–related bleeding from a hypoplastic portal venous system. Answer choices *a, b, d,* and *e* are less likely given this patient's characteristics and clinical presentation.

IV.21. Answer a.
Management of an acute porphyric attack consists of quickly identifying and reversing the precipitating factors. Acetaminophen, meperidine, and morphine can be used safely for pain management. Ondansetron is the preferred antiemetic, and use of promethazine

should be avoided. IV glucose is beneficial. The definitive treatment of an acute porphyric attack is IV hemin (answer choice *a*), which replenishes the depleted heme pool and ameliorates signs and symptoms of the acute porphyric attack. IV albumin (answer choice *e*) is not used in the treatment of acute porphyria.

IV.22. Answer c.
This case of scleroderma is complicated by CIPO. Intestinal stasis from CIPO can result in recurrent obstructive symptoms mimicking mechanical bowel obstruction and cause SIBO. Initial therapy for SIBO is oral antibiotics (eg, ciprofloxacin) for 7 to 10 days (answer choice *c*). Low-dose octreotide (25-50 mcg subcutaneously every evening) may reduce bacterial overgrowth and relieve symptoms by inducing the intestinal migrating motor complex. High-dose octreotide (answer choice *d*) does not increase small intestinal motility like low-dose octreotide and will potentially worsen stasis and obstructive symptoms. Localized small-bowel involvement in scleroderma and short dysfunctional segments can be resected with good outcomes (answer choice *a*); however, this patient has diffuse small-bowel involvement, precluding this approach. Total parenteral nutrition (answer choice *e*) may be considered when pharmacologic treatment fails. Intestinal transplant (answer choice *b*) would be considered only in severe, refractory cases of CIPO when complications such as hepatic failure and recurrent sepsis occur with total parenteral nutrition.

IV.23. Answer c.
This is a case of ELP manifesting with a small-caliber esophagus and endoscopic findings mimicking eosinophilic esophagitis. Although they may have similar symptoms, radiographic findings, and endoscopic changes, these 2 conditions differ in several ways. First, both conditions are seen in demographically different populations, with ELP occurring almost exclusively in middle-aged women and eosinophilic esophagitis seen mainly in young men. The predominant site of esophageal stricture formation is different, with the proximal esophagus being the most common site of involvement in ELP and there being no predilection in eosinophilic esophagitis. The histopathology of the 2 conditions differs in that ELP shows a dense subepithelial lymphocytic infiltrate, intraepithelial lymphocytes, and multiple eosinophilic necrotic keratinocytes, whereas a predominant eosinophilic infiltrate is seen with eosinophilic esophagitis. Eosinophilic esophagitis responds to treatment with acid-suppressive medications or topical corticosteroids, whereas there is no consensus on the best approach to treatment of ELP, with reported therapies including systemic or topical corticosteroids, topical tacrolimus, and endoscopic corticosteroid injection. Gastroesophageal reflux disease (answer choice *a*), epidermolysis bullosa (answer choice *d*), and esophageal Crohn disease (answer choice *e*) are incorrect since patients with these conditions would not present with a small-caliber esophagus and mucosal rings.

IV.24. Answer c.
GI disease in amyloidosis results from either mucosal or neuromuscular infiltration of the gut. Within the GI tract, the most common site of infiltration is the descending duodenum (100%), followed by the colorectum (>90%) and the esophagus (70%).

V

Colon

14

Inflammatory Bowel Disease: Clinical Aspects

DAVID H. BRUINING, MD

Inflammatory bowel disease (IBD) remains a vexing clinical challenge. It is a disease process characterized by chronic idiopathic intestinal inflammation. The 2 main subtypes are ulcerative colitis (UC) and Crohn disease (CD). UC involves the colonic mucosa, extending proximally from the anal verge in an uninterrupted pattern to involve all or part of the colon. In contrast, CD is a transmural process with a special predilection for small-bowel involvement. However, CD can occur anywhere in the gastrointestinal tract from mouth to anus, manifesting as patchy inflammation with intervening areas of normal mucosa. *Indeterminate colitis* occurs in a small number of IBD patients who have chronic colon inflammation that has features consistent with both UC and CD. All 3 of these diseases—UC, CD, and indeterminate colitis—can be associated with extraintestinal disease manifestations.

Epidemiology

Men and women generally have a similar risk of IBD, but the overall incidence of CD is higher for females. Onset of IBD is most frequent among adolescents; the peak incidence is between ages 15 and 25 years, with a smaller second peak between the fifth and seventh decades. IBD is more common among Ashkenazi Jews than among non-Jews. Historically, UC has been more common than CD.

The incidence of UC is 8.3 per 100,000 person-years in Olmsted County, Minnesota, and 14.2 per 100,000 person-years in Winnipeg, Manitoba. The prevalence in Olmsted County is 229 per 100,000 persons. The proportion of patients with ulcerative proctitis varies in different series from 17% to 49% of the totals.

The incidence of CD also varies among reporting centers. It is 6.9 per 100,000 person-years in Olmsted County and 14.6 per 100,000 person-years in Winnipeg. The prevalence in Olmsted County is 133 per 100,000 persons.

Mortality rates for persons with IBD may be slightly higher than those for the general population. In a study from Stockholm, the standardized mortality ratio was 1.37 for UC and 1.51 for CD.

Genetics

The genetic influence on the development of IBD is a topic of considerable interest. Between 10% and 15% of patients with UC have a relative with IBD, mainly UC and, less commonly, CD. Approximately 15% of patients with CD have a relative with IBD, mainly CD and, less commonly, UC. The phenotypic concordance appears to be higher for CD. Several genetic linkages have been identified, and specific genetic defects have been determined in IBD. The first to be characterized was the *CARD15*/*NOD2* gene, present in the homozygous form in up to 17% of patients with CD. This genetic defect is associated with fibrostenotic disease involving the distal ileum. Other associations are with the *IBD5* haplotype of chromosome 5 and the *IL23R* gene on chromosome 1p31. The latter gene encodes a proinflammatory cytokine, interleukin 23. Three genetic syndromes are associated with IBD: Turner syndrome, Hermansky-Pudlak syndrome (oculocutaneous albinism, a platelet aggregation defect, and a ceroid-like pigment deposition), and glycogen storage disease type IB.

Diet

Patients with IBD have no specific dietary restrictions. Although lactose intolerance is more common among patients with CD

Abbreviations: ASCA, anti–*Saccharomyces cerevisiae* antibody; CD, Crohn disease; CT, computed tomography; IBD, inflammatory bowel disease; MR, magnetic resonance; pANCA, perinuclear antineutrophil cytoplasmic antibody; UC, ulcerative colitis

than among the general population, lactose and other milk components do not seem to influence the inflammatory disease. Elemental diets and parenteral hyperalimentation are useful for correction of malnutrition and for growth failure in children with IBD. Parenteral nutrition has not been found to be superior to enteral nutrition for CD. The use of enteral nutrition or parenteral nutrition as primary therapy for CD is controversial; nutritional support is used primarily as an alternative to corticosteroids. There is no convincing evidence that elemental nutrition or parenteral nutrition is therapeutic for UC.

Pregnancy

Fertility is normal in patients with inactive IBD. Fertility is decreased in some women with active IBD, but most patients are able to conceive. Sulfasalazine causes reversible infertility in men as a result of abnormalities of spermatogenesis and decreased sperm motility. There is debate about the risk of birth defects in the offspring of a parent with IBD. Most studies do not show an increased risk in association with the disease or the treatments; however, methotrexate is contraindicated during pregnancy (its use should be discontinued ≥3 months before conception). The course of pregnancy is usually normal, although there is an increased chance of preterm delivery and decreased birth weight. Two-thirds of women with IBD in remission before pregnancy remain in remission through pregnancy and the postpartum period. Flares occur most commonly during the first trimester and the postpartum period. Previous colectomy with an end-ileostomy or with a continent ileal pouch does not preclude pregnancy, and for some women, vaginal delivery is still an option. Increased infertility has been reported in women after ileal pouch–anal anastomosis for UC. There is no definitive evidence to support the idea that breastfeeding is a protective factor against later development of IBD.

Environmental Influences

UC is primarily a disease of nonsmokers. Only 13% of patients with UC are current smokers, and the rest are nonsmokers or former smokers. Pouchitis after proctocolectomy with an ileal J-pouch–anal anastomosis for UC is less common among smokers. In contrast, patients with CD are more commonly smokers than the general population, and smoking increases the risk of symptomatic recurrences. IBD is more common in colder climates than in warmer climates, and it is more common in developed countries than in developing countries.

Diagnosis

The diagnosis of IBD is confirmed by a combination of endoscopic, radiographic, serologic, and pathology studies. The specific diagnostic tests are based on the presenting symptoms and physical examination findings.

Clinical Presentations

Ulcerative Colitis

The onset of UC may be gradual or sudden, with an increase in bowel movements and bloody diarrhea, fecal urgency, cramping abdominal pain, and fever. The course is variable, with periods of exacerbation, improvement, and remission that may occur with or without specific medical therapy. About half of the patients have disease involving the left side of the colon to some extent, including proctitis, proctosigmoiditis, and disease extending from the splenic flexure distally. Constipation with rectal bleeding is a presenting symptom in about 25% of patients with disease limited to the rectum. Diarrhea may vary from 1 to 20 or more loose or liquid stools daily, usually worse in the morning and immediately after meals, and patients with moderate or severe symptoms often have nocturnal stools. Abdominal pain is usually cramping, which is worse after meals or bowel movements. Anorexia, weight loss, and nausea in the absence of bowel obstruction are common with severe and extensive disease but uncommon with mild to moderate disease or disease limited to the left colon. In children, urgency, incontinence, and upper gastrointestinal tract symptoms are more frequent and growth failure is common. Extraintestinal symptoms occur in up to 36% of patients.

Crohn Disease

Symptoms of CD depend on the anatomical location of the disease. With ileocecal disease, abdominal pain, diarrhea, and fever are typical. With colonic disease, bloody bowel movements with diarrhea, weight loss, and low-grade fever are common. Patients with gastroduodenal CD often have burning epigastric pain and early satiety, and these symptoms usually overshadow the symptoms from coexisting ileal or colonic disease. The symptoms of oral or esophageal CD include dysphagia, odynophagia, and chest pain, even without eating. The findings in patients with perianal CD include perirectal abscesses, painful and edematous external hemorrhoids, and anal and perianal fistulas. Enterovesical fistulas can cause pneumaturia and recurrent polymicrobial urinary tract infections. Rectovaginal fistulas occur in up to 10% of women with rectal CD and may cause gas or stool to be passed from the vagina. In children, the onset of CD is often insidious; weight loss occurs in up to 87% before the diagnosis is made, and 30% of children have growth failure before the onset of intestinal symptoms.

Physical Examination

In mildly active UC, physical examination findings are often normal or there may be abdominal tenderness, particularly with palpation over the sigmoid colon. Patients with more severe disease may have pallor (anemia), tachycardia (dehydration), fever, diminished bowel sounds, and diffuse abdominal tenderness with rebound. Tenderness with rebound is ominous and suggests toxic dilatation or perforation. In CD, physical examination findings may be normal or may include 1 or more of the following: fever, weight loss, muscle wasting, abdominal tenderness (particularly in the lower abdomen), and a palpable mass, usually in the ileocecal region of the right lower abdomen. Rectal examination may show large, edematous, external hemorrhoidal tags; fistulas; anal canal fissures; and anal stenosis. Ulcers in CD may occur on the lips, gingiva, or buccal mucosa.

Laboratory Findings

In mild disease, laboratory results may be normal. Iron deficiency anemia due to gastrointestinal tract blood loss may occur in UC and in CD, and anemia of chronic disease, presumably due to cytokine effects on the bone marrow, may occur with either disorder. Malabsorption of vitamin B_{12} or folate is an additional cause of anemia in patients with CD. Hypoalbuminemia, hypokalemia, and metabolic acidosis can occur with severe disease because of potassium and bicarbonate wasting with diarrhea. An increased

leukocyte count may be a consequence of active IBD or be due to a complicating abscess.

Laboratory values of acute phase reactants, including the erythrocyte sedimentation rate and C-reactive protein, can be increased but may also be normal in mildly active disease. The perinuclear antineutrophil cytoplasmic antibody (pANCA) is positive in about two-thirds of patients with UC and in about one-third of patients with CD. The anti–*Saccharomyces cerevisiae* antibody (ASCA) test is positive in about two-thirds of patients with CD and in about one-third of patients with UC. These tests may be used together to help distinguish between UC and CD. However, the positive predictive value of the 2 tests together is 63.6% for UC and 80% for CD; thus, distinguishing the 2 diseases with these serologic tests is less than ideal (Table 14.1). Several additional antimicrobial antibodies have been described, including *Escherichia coli* outer membrane protein C (OmpC), *Bacteroides caccae* TonB-linked outer membrane protein W (OmpW), antibodies to CBir1 flagellin (anti-CBir1), and *Pseudomonas fluorescens*–related protein (anti-I2). The usefulness and role of these markers in IBD diagnostic and management algorithms is being assessed. With new-onset IBD or at relapse, infection should be ruled out with stool studies, including cultures for bacterial pathogens and examinations for ova and parasites and *Clostridium difficile* toxin. For patients with systemic symptoms such as fever, malaise, and myalgias, cytomegalovirus infection should be excluded by mucosal biopsy studies, particularly if the patient is receiving therapy with immunosuppressive agents.

Endoscopy

Flexible proctosigmoidoscopy or colonoscopy can identify characteristic mucosal changes of UC, including loss of the normal vascular markings, mucosal granularity, friability, mucous exudate, and focal ulceration (Figure 14.1). With colonoscopy, the extent of disease can be determined and the terminal ileum can be examined for evidence of backwash ileitis in UC or ileal involvement in CD. Patients with left-sided UC may have inflammatory changes around the appendix, referred to as a *cecal patch*, as a manifestation of the disease; this finding should not be confused with segmental colitis due to CD. Only a limited examination of the rectosigmoid colon should be performed in patients with severely active colitis because of the risk of perforation. In CD, characteristic lesions at colonoscopy are deep linear ulcers (rake ulcers) with surrounding erythema and granularity and skip areas of normal-appearing mucosa between areas of involvement (Figure 14.2). Upper gastrointestinal endoscopy can confirm the presence and distribution of disease in the upper gut and define how severely the mucosa is affected.

For patients with IBD who have extensive, long-standing colonic inflammation, the risk of malignancy is higher than that for the general population. For that reason, periodic colonoscopy with surveillance biopsies for dysplasia is indicated after 8 to 10 years of disease for patients who have extensive UC. The risk of malignancy for patients with less extensive UC (with involvement of the colon distal to the splenic flexure) also is increased, but the magnitude of the risk has not been defined. The risk of rectal cancer for patients with ulcerative proctitis without colitis above the rectum does not appear to be increased. Patients with either form of colitis, involving more than one-third of the colon, should have periodic surveillance biopsies after 8 to 10 years of disease. The optimal interval between surveillance examinations has not been defined, and the examinations are usually performed at 1- to 2-year intervals.

Table 14.1. Positive Predictive Value of Serologic Markers in Patients With Indeterminate Colitis

Disease	*Marker*	*Positive Predictive Value, %*
Ulcerative colitis	pANCA+ ASCA–	63.6
Crohn disease	pANCA– ASCA+	80

Abbreviations: ASCA, anti–*Saccharomyces cerevisiae* antibody; pANCA, perinuclear antineutrophil cytoplasmic antibody.

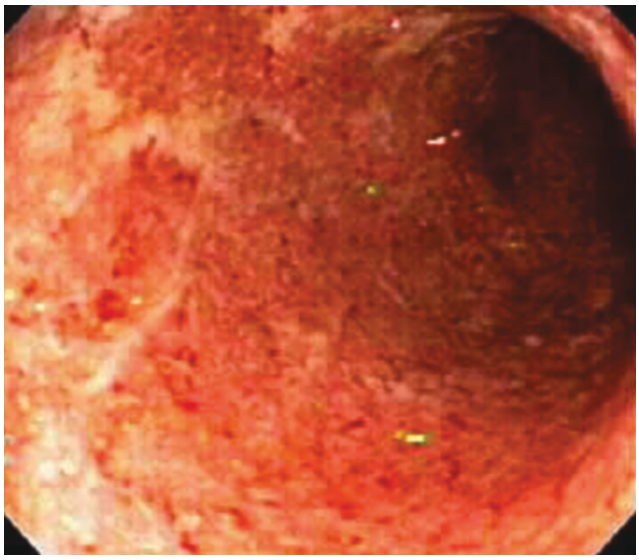


Figure 14.1. Ulcerative Colitis. Colonoscopy shows diffuse changes of colitis with mucosal granularity, erythema, and exudate. This is typical of moderately active ulcerative colitis.

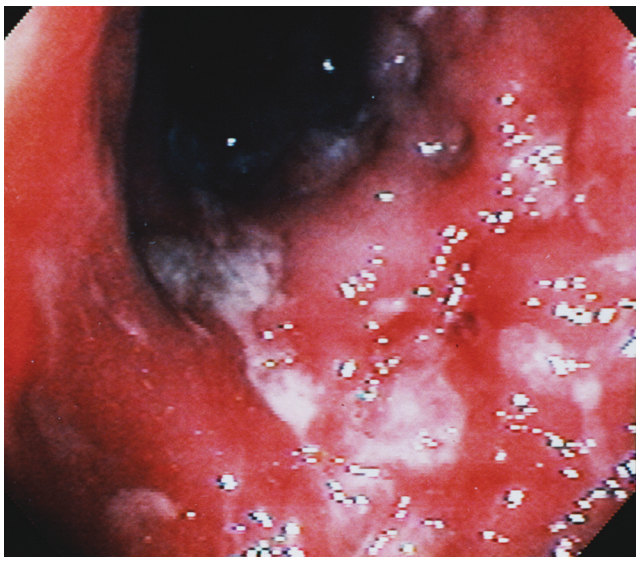


Figure 14.2. Crohn Disease. Colonoscopy shows linear ulcers and surrounding mucosal erythema, edema, and granularity. This is typical of Crohn disease.

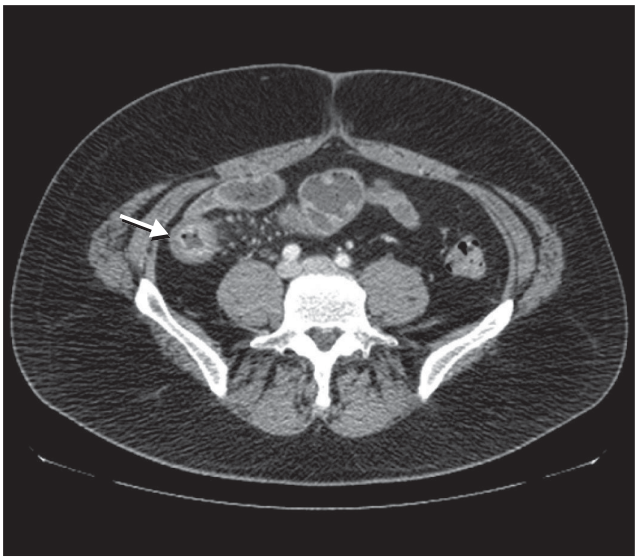


Figure 14.3. Computed Tomographic Enterography in Crohn Disease. This image shows wall thickening and mural enhancement (arrow) in the terminal ileum of a patient with active Crohn disease.

Radiologic Features

Plain abdominal films with supine and upright views should be obtained in cases of severely active colitis to examine for complications, including perforation with free air or toxic dilatation. In CD, computed tomographic (CT) enterography (Figure 14.3) or magnetic resonance (MR) enterography (Figure 14.4) can assess the location and extent of small-bowel disease and complications such as fistulas, strictures, or abscesses. CT enterography has been shown to have superior sensitivity and specificity compared with traditional small-bowel follow-through images for detecting active small intestinal inflammation. MR enterography has the advantage of avoiding exposure to ionizing radiation and is safe in pregnancy (gadolinium should be avoided in the first trimester). Wireless capsule endoscopy may have a role in evaluating some patients but should not be performed if obstructive or stricturing disease is suspected, because of the risk of capsule retention. A barium swallow may be useful for assessment of CD that involves the esophagus, stomach, and duodenum. MR imaging is the preferred imaging method for identifying pelvic and perianal abscesses.

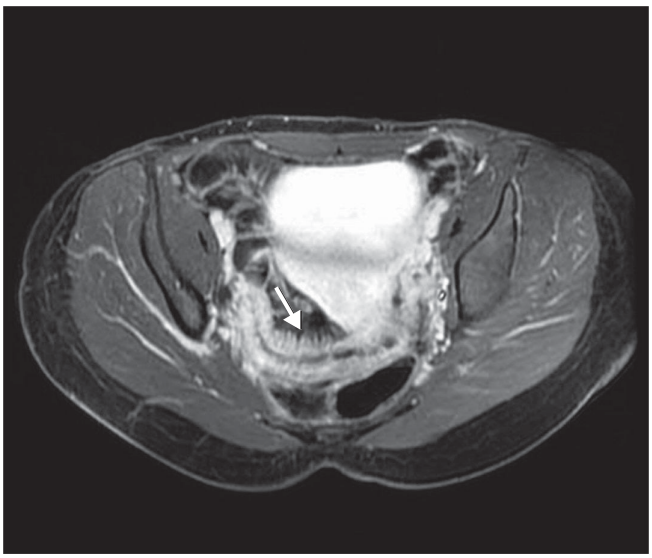


Figure 14.4. Magnetic Resonance Enterography in Crohn Disease. A segment of ileum shows enhancement, thickening, and dilated vasa recta (arrow) (the comb sign) in a patient with Crohn disease.

Histology

Mucosal biopsy specimens from involved areas of the gastrointestinal tract are useful for excluding self-limited colitis and other infections and noninfectious colitis causes, such as ischemia, drug effect, radiation injury, and solitary rectal ulcer syndrome. Noncaseating granulomas are a feature of CD and can be helpful in differentiating it from UC, but even when multiple specimens are taken, granulomas are identified in only 30% of specimens of resected CD. The presence of focal, patchy inflammation is characteristic of CD but not invariably identifiable.

Differential Diagnosis

UC and CD must be differentiated from infectious causes of colitis and also from the noninfectious causes of inflammation in the colon and small intestine (Box 14.1). *Microscopic colitis*

Box 14.1. Differential Diagnosis of Inflammatory Bowel Disease

Acute self-limited colitis

- Bacteria
  - Toxigenic *Escherichia coli*
  - *Salmonella*
  - *Shigella*
  - *Campylobacter*
  - *Yersinia*
  - *Mycobacterium*
  - *Neisseria gonorrhoeae*
  - *Clostridium difficile*
  - *Chlamydia*
- Parasites
  - Amebae
- Viruses
  - Cytomegalovirus
  - Herpes simplex

Collagenous colitis and lymphocytic colitis

Diverticular disease–associated colitis

Medication-induced colitis

- Nonsteroidal antiinflammatory drugs
- Gold

Ischemic colitis

Radiation enterocolitis

Diverticulitis

Appendicitis

Neutropenic enterocolitis

Solitary rectal ulcer syndrome

Malignancy

- Carcinoma
- Lymphoma
- Leukemia

describes a syndrome of chronic watery diarrhea with characteristic histologic abnormalities but without specific endoscopic or radiographic features. Specific forms of microscopic colitis include lymphocytic colitis, in which intraepithelial lymphocytes and chronic inflammatory cells are present in the lamina propria, and collagenous colitis, which includes the features of lymphocytic colitis plus the presence of a subepithelial collagen band. Diverticular disease–associated chronic colitis is a segmental colitis in which there are chronic inflammatory changes of the mucosa limited to areas of the sigmoid colon where diverticula are present.

Nonsteroidal antiinflammatory drugs can cause ulcerations throughout the gastrointestinal tract, including the colon and rectum, which can be confused with CD. Ischemia more commonly causes segmental colitis that may be confused with CD, but occasionally it causes a diffuse colitis that can resemble UC. Injury to the rectum from radiotherapy for prostate cancer or gynecologic malignancy may appear similar to ulcerative proctitis or CD with fistulas and strictures. Injury to the small intestine and more proximal colon from radiotherapy may cause chronic diarrhea, strictures, malabsorption, and other features that may mimic extensive CD. Solitary rectal ulcer syndrome may be confused with CD involving the rectum but can be differentiated on the basis of histologic features showing marked subepithelial fibrosis without inflammation. Diverticulitis may be confused with CD when patients present with fistulas, localized abscesses, and a segmental colitis.

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15

Inflammatory Bowel Disease: Therapy

DARRELL S. PARDI, MD

Many therapies are available for patients with inflammatory bowel disease (IBD). Medical therapies include aminosalicylate drugs such as sulfasalazine, olsalazine, balsalazide, and various formulations of mesalamine; antibiotics; corticosteroids; immunosuppressive medications such as azathioprine, 6-mercaptopurine (6-MP), methotrexate, and cyclosporine; and biotechnology medications such as anti–tumor necrosis factor (TNF) agents and newer agents with different mechanisms of action. This chapter reviews these various treatments and their positions in the treatment algorithms for Crohn disease and ulcerative colitis. Many surgical therapies also are used in patients with IBD, although a detailed review of these options is beyond the scope of this chapter.

Many of the treatments reviewed are used for both ulcerative colitis and Crohn disease, with some notable exceptions. Some of the treatments are designed to deliver medication to specific areas of the bowel, while others act systemically. For the former, a thorough understanding of the anatomical distribution of inflammation is required in order to choose the optimal drug for a given patient.

Ulcerative colitis can be divided into *ulcerative proctitis* (rectal involvement only), *ulcerative proctosigmoiditis* (involving the rectum and sigmoid colon), *left-sided ulcerative colitis* (inflammation from the rectum to the splenic flexure), and *extensive colitis* or *pancolitis* (inflammation extends from the rectum to beyond the splenic flexure or involves the entire colon). Most cases of luminal Crohn disease can be divided into *ileitis, colitis*, and *ileocolitis*. Much less common is involvement of the jejunum or the upper gastrointestinal tract. A subset of patients has perianal disease with fissures, fistulas, abscesses, and other findings.

Abbreviations: 5-ASA, 5-aminosalicylate; IBD, inflammatory bowel disease; IPAA, ileal pouch–anal anastomosis; MMX, multimatrix system; 6-MP, 6-mercaptopurine; PML, progressive multifocal leukoencephalopathy; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase

Aminosalicylates

Sulfasalazine, oral mesalamine (Pentasa, Asacol, Delzicol, Lialda, and Apriso), rectal mesalamine (Rowasa and Canasa), olsalazine, and balsalazide (Colazal and Giazo) are drugs that deliver 5-aminosalicylate (5-ASA) to the bowel lumen (Table 15.1). With the exception of the Pentasa formulation of mesalamine, these medications primarily deliver drug to the colon.

Sulfasalazine, the first drug developed in this class, combines a 5-ASA molecule with sulfapyridine. This drug was originally developed to treat rheumatoid arthritis, and for that indication, the sulfapyridine moiety is thought to be the active component. Subsequently, sulfasalazine was discovered to be effective for ulcerative colitis, with the active ingredient being 5-ASA. This discovery led to the development of the newer generation of 5-ASA drugs that have fewer side effects than the sulfa-containing parent drug. In sulfasalazine, 5-ASA is linked to sulfapyridine by an azo bond, which keeps the 5-ASA inactivated until the azo bond, is cleaved by bacterial enzymes. Therefore, active drug is delivered primarily to the colon.

Olsalazine and balsalazide are prodrugs with 5-ASA bound by an azo bond. In addition, 5-ASA is available covered with a pH-dependent polymer that dissolves in the terminal ileum and cecum (Asacol and Delzicol); as ethylcellulose-coated granules that release drug throughout the gastrointestinal tract (Pentasa); or in more complex delivery systems that result in prolonged mesalamine release throughout the colon (Lialda and Apriso). Mesalamine can also be administered as an enema to treat

Table 15.1. Preparations of 5-Aminosalicylate (5-ASA) for Treating Ulcerative Colitis

Generic Name	*Proprietary Name*	*Formulation*	*Sites of Delivery*	*Daily Dose, g*[a]	
				Active	*Maintenance*
Mesalamine (5-ASA)	Rowasa	Enema suspension	From rectum to splenic flexure	4	4[b]
	Canasa	Suppository	Rectum	1	1[b]
	Pentasa	Ethylcellulose-coated granules (controlled-release)	Duodenum, jejunum, ileum, colon	2-4	1.5-4
	Asacol	Eudragit-S–coated tablets (dissolves at pH ≥7.0)	Terminal ileum, colon	2.4-4.8	1.6-4.8
	Delzicol	Eudragit-S–coated tablets (dissolves at pH ≥7.0)	Terminal ileum, colon	2.4-4.8	1.6-4.8
	Apriso	Enteric coating (dissolves at pH ≥6) around polymer matrix	Terminal ileum, colon	1.5	1.5
	Lialda	Enteric coating (dissolves at pH ≥7) around polymer matrix with lipophilic and hydrophilic matrices	Terminal ileum, colon	2.4-4.8	2.4
Olsalazine	Dipentum	5-ASA dimer linked by azo bond	Colon	2-3	1
Sulfasalazine	Azulfidine	5-ASA linked to sulfapyridine by azo bond	Colon	2-4	2-4
Balsalazide	Colazal	5-ASA linked to inert carrier by azo bond	Colon	6.75	4.5-6.75
	Giazo	5-ASA linked to inert carrier by azo bond	Colon	6.6	4.4-6.6

[a] Dose ranges reflect those commonly used in clinical practice and are broader than those specifically studied in clinical trials.
[b] When 5-ASA enemas or suppositories are used for maintenance therapy, the dose may be decreased to every second or third night.

left-sided colitis or proctosigmoiditis (Rowasa) or as a suppository to treat proctitis (Canasa).

All 5-ASA drugs are effective in inducing and maintaining remission in mildly to moderately active ulcerative colitis. The choice of drug therefore depends primarily on the distribution of inflammation. In contrast, the efficacy of 5-ASA drugs for Crohn disease is much less clear, with a recent meta-analysis concluding that these drugs have little or no benefit over placebo. Drug-associated toxicity is common with sulfasalazine, including headache, epigastric pain, nausea and vomiting, and skin rash. Less common but severe adverse events include hepatitis, fever, autoimmune hemolysis, bone marrow toxicity, and others. Folate deficiency is induced by sulfasalazine, and therefore folate supplementation is required. Reversible male infertility may occur. Sulfasalazine may be taken during pregnancy and breastfeeding.

Olsalazine, balsalazide, and mesalamine generally are better tolerated than sulfasalazine. Commonly occurring adverse events include headache, rash, and alopecia. Less common is a hypersensitivity reaction resulting in worsening diarrhea and abdominal pain that may be confused with a colitis flare. Rarely, serious adverse events occur, including interstitial nephritis, pericarditis, pneumonitis, hepatitis, or pancreatitis. Periodic monitoring of renal function is recommended with long-term treatment with any mesalamine formulation, although nephrotoxicity is rare. A secretory diarrhea can occur with olsalazine, which has limited its use. Olsalazine, balsalazide, and mesalamine may be taken during pregnancy and breastfeeding.

Antibiotics

Controlled trials of various antibiotics have not demonstrated efficacy in treating ulcerative colitis. The data for use of antibiotics in Crohn disease are less clear cut. Three small studies suggested efficacy of metronidazole and ciprofloxacin; however, a placebo-controlled trial of metronidazole did not demonstrate efficacy for inducing remission in active Crohn disease. Similarly, another trial did not demonstrate an adjunctive role for antibiotics in patients receiving budesonide for active Crohn disease. Controlled trials of metronidazole and ornidazole after ileal resection showed that postoperative endoscopic recurrence of disease could be delayed after resection for Crohn disease, although side effects were common; findings from a small pilot study of ciprofloxacin after ileal resection were negative. Because of these results, the use of antibiotic therapy for Crohn disease is debated, and in the absence of penetrating complications, such as a fistula or abscess, the role of antibiotics as primary therapy in Crohn disease is limited.

In contrast, uncontrolled studies and clinical experience indicate that antibiotics such as metronidazole and ciprofloxacin are effective for fistulizing Crohn disease, particularly perianal fistulas. No controlled trials have been performed, but antibiotic therapy is used widely for this treatment indication and is considered to be the first-line therapy in combination with immunosuppressive or biological therapies.

Small placebo-controlled and comparative trials have shown that metronidazole and ciprofloxacin are effective for inducing remission in patients with acute pouchitis after colectomy and ileoanal anastomosis for ulcerative colitis. Uncontrolled clinical observations have suggested that metronidazole and ciprofloxacin may be effective for maintaining remission in patients with chronic pouchitis.

Adverse events observed with metronidazole include paresthesias, peripheral neuropathy, yeast infections, anorexia, dyspepsia, nausea, a metallic taste, and intolerance to alcohol. Adverse events observed with ciprofloxacin are less common and include photosensitivity, nausea, rash, increased liver enzymes, and tendinopathy, rarely including tendon rupture. Ciprofloxacin should not be taken during pregnancy or breastfeeding. Metronidazole can be considered during pregnancy, but it is secreted in breast milk.

Corticosteroids

Corticosteroids are commonly used in patients with IBD. A dose-response study of patients with active ulcerative colitis showed that a prednisone dosage of 40 or 60 mg daily is more effective than 20 mg daily, with more adverse events with a 60-mg dose. Doses larger than 60 mg provide little if any additional efficacy, with more side effects, and should not be used. Similar data exist for corticosteroid therapy in patients with Crohn disease. Most clinicians initiate oral corticosteroid therapy with prednisone at a dosage of 40 to 60 mg daily. For patients with ileocolonic Crohn disease, controlled ileal-release budesonide is an alternative to prednisone, and for patients with ulcerative colitis,

a colonic-release formulation of budesonide (multimatrix system [MMX] budesonide) is now available. Both formulations of budesonide offer effective therapy with fewer steroid-related side effects (owing to high first-pass hepatic metabolism), although at a higher cost.

Placebo-controlled trials have shown that corticosteroid therapy is not effective for maintaining remission in ulcerative colitis or Crohn disease; thus, for patients who respond to steroid therapy, the dose is typically tapered over 2 to 4 months while use of another medication is begun for maintenance. Patients with severely active disease who do not respond to oral corticosteroid therapy are often either hospitalized and given corticosteroids intravenously (eg, methylprednisolone, 40-60 mg daily) or treated with a biological agent.

Corticosteroid enemas are effective for inducing remission in left-sided ulcerative colitis or ulcerative proctosigmoiditis, and corticosteroid suppositories are effective for ulcerative proctitis. However, in clinical trials, topical mesalamine is superior to topical corticosteroids, and thus topical corticosteroids are typically reserved for patients who do not tolerate or respond to mesalamine. Topical corticosteroids are not effective for maintaining remission.

Short- and long-term adverse events occur frequently in patients receiving corticosteroids. Short-term adverse events include weight gain, moon face, acne, ecchymoses, hypertension, hirsutism, petechial bleeding, striae, and psychosis. Long-term adverse events include diabetes mellitus, increased risk of infection, osteonecrosis, osteoporosis, myopathy, cataracts, and glaucoma, among many others. Corticosteroids may be taken during pregnancy and breastfeeding.

Azathioprine and 6-MP

Azathioprine is a prodrug that is converted rapidly to 6-MP, which is then either inactivated (to 6-thiouric acid by xanthine oxidase or to 6-methylmercaptopurine by thiopurine methyltransferase) or activated through several enzyme steps to the active metabolite 6-thioguanine nucleotide. The enzyme activity of thiopurine methyltransferase (TPMT) is determined genetically: 1 in 300 patients (0.3%) have no enzyme activity and have a very high risk of serious toxicity, such that these drugs should not be used; 10% have intermediate enzyme activity, with an increased risk of toxicity that can be mitigated in most patients by dose reduction and careful follow-up; and 90% have normal enzyme activity. It is recommended that all patients be tested for TPMT activity before receiving these medications, and those with normal TPMT activity be treated with full-dose azathioprine or 6-MP.

Trials have shown that azathioprine at dosages of 1.5 to 2.5 mg/kg daily is effective for steroid sparing and maintaining remission in ulcerative colitis. One study showed that azathioprine 2.0 mg/kg daily was more effective than oral mesalamine 3.2 g daily. Trials also have shown that azathioprine 2 to 3 mg/kg daily and 6-MP 1.5 mg/kg daily are effective for inducing remission, closing fistulas, steroid sparing, and maintaining remission in Crohn disease.

Adverse events with azathioprine and 6-MP include fever, nausea, allergic reactions, pancreatitis, arthralgias, bone marrow suppression, hepatitis, infectious complications, and an increased risk of lymphoma and skin cancer. Although azathioprine and 6-MP are classified as pregnancy category D drugs, several recent publications indicated that these drugs can be administered safely during pregnancy. They are also probably safe for use during breastfeeding.

Methotrexate

Low-dose oral methotrexate (12.5 mg weekly) is not effective in ulcerative colitis or Crohn disease. In contrast, higher-dose (25 mg weekly) parenteral methotrexate is effective for inducing and maintaining remission in Crohn disease. Adverse events that may occur with methotrexate include rash, nausea, mucositis, diarrhea, bone marrow suppression, infections, pneumonitis, increased liver enzymes, and liver fibrosis or cirrhosis. Some toxicity can be mitigated by the concomitant administration of folic acid. Methotrexate is contraindicated for pregnant and lactating women.

Cyclosporine

Intravenous cyclosporine is effective for inducing remission in patients with severely active, steroid-refractory ulcerative colitis. The efficacy of cyclosporine at a moderate dose (2 mg/kg) is similar to that at a higher dose (4 mg/kg). Many patients who respond to cyclosporine undergo a colectomy within a few years; therefore, many clinicians do not feel the risk is worth the long-term benefit. Placebo-controlled trials of oral cyclosporine did not demonstrate efficacy for inducing or maintaining remission in Crohn disease.

Adverse events that may occur with cyclosporine therapy include headache, tremor, paresthesias, seizures, hypertrichosis, gingival hyperplasia, renal insufficiency, hypertension, infections, hepatotoxicity, and nausea and vomiting. Cyclosporine is generally avoided in pregnant women.

Anti-TNF Agents

Infliximab is a mouse-human chimeric, intravenously administered monoclonal antibody directed toward TNF-α. Adalimumab and golimumab are fully human monoclonal antibodies and certolizumab pegol is a pegylated humanized (mostly human) Fab′ fragment; all 3 are administered by subcutaneous injection. Controlled trials have shown that infliximab is effective for inducing and maintaining remission and closing fistulas in Crohn disease and for inducing and maintaining remission in ulcerative colitis. Controlled trials have shown that adalimumab and certolizumab pegol are effective for inducing and maintaining remission in Crohn disease and ulcerative colitis. Data also indicate that adalimumab and certolizumab can result in fistula closure. Controlled trials have shown that golimumab is effective for inducing and maintaining remission in ulcerative colitis.

Adverse events that may occur with anti-TNF therapy include formation of antibodies against the therapy, infusion or injection site reactions, delayed hypersensitivity reactions, autoantibody formation, drug-induced lupus, infection (particularly tuberculosis and fungal infections such as histoplasmosis), psoriasis, and possibly lymphoma and skin cancers. Antibodies to infliximab lead to higher rates of infusion reactions and loss of efficacy in patients receiving infliximab. The frequency of formation of these antibodies is decreased when patients receive 3 induction doses of infliximab followed by maintenance infusions every 8 weeks, with concomitant immunosuppressive therapy and pretreatment with corticosteroids before each dose. There are fewer studies and less experience with antibodies to adalimumab, certolizumab, or golimumab. Although data are limited, anti-TNF agents appear to be safe for use in pregnant women.

Natalizumab

Natalizumab is a humanized IgG4 monoclonal antibody to α_4 integrin. Placebo-controlled trials have shown that it is effective for induction and maintenance of remission in Crohn disease. Natalizumab is associated with infectious complications, including the development of progressive multifocal leukoencephalopathy (PML), a predominantly fatal infection of the central nervous system caused by the JC polyomavirus. This risk appears to be 1 in 1,000 patients overall. The development of a test for antibodies to the JC polyomavirus has renewed interest in the use of natalizumab for patients with Crohn disease, since patients who are seronegative appear to have a very low risk of PML. In those who are seropositive, the risk of PML is unacceptably high, particularly among patients who have been treated with immunosuppressive agents.

Surgery

The original operation for ulcerative colitis consisted of a total proctocolectomy with Brooke ileostomy (Figure 15.1). In the 1970s, the continent ileostomy, or Kock pouch, served as an alternative to the conventional ileostomy (Figure 15.1). However, dysfunction of the pouch, often requiring reoperation, was common. In the 1980s, the ileal pouch–anal anastomosis (IPAA) largely replaced the Kock pouch for patients with ulcerative colitis who required operation and is now the standard procedure for the majority of patients (Figure 15.1).

Colectomy is indicated for patients with ulcerative colitis who have colorectal cancer or dysplasia, patients who have disease refractory to medical therapy, and patients who have a complication (such as toxic megacolon). Colectomy for low-grade dysplasia has been the subject of debate recently because of results from newer studies, and the procedure is dependent on other patient factors. Patients who elect not to proceed with colectomy should have more intensive surveillance colonoscopy and biopsies, ideally with chromoendoscopy, which increases the detection of dysplasia.

The most common complication after IPAA for ulcerative colitis is pouchitis, which is characterized by diarrhea, cramps, urgency, and often fecal incontinence. The cumulative frequency of acute pouchitis after IPAA for ulcerative colitis approaches 50% by 5 years. Most cases respond to a short course of antibiotics (often ciprofloxacin or metronidazole), although some patients have a prompt recurrence after discontinuation of the antibiotic (termed antibiotic-dependent chronic pouchitis). In these patients, chronic suppressive antibiotics can be helpful. A small subset of patients have antibiotic-refractory chronic pouchitis and require treatment with steroids (eg, budesonide), immunomodulatory medications, biologicals, or surgery (pouch excision or diversion). In this group of patients, the possibility of Crohn disease of the pouch must be considered.

The probability of surgical resection in patients with Crohn disease increases with time. By 15 years after diagnosis, 70% of patients have had at least 1 operation, and half of these have had 2 or more operations, but much of the data on surgical natural history of Crohn disease are from the era before biologicals. Emerging data indicate that these highly effective medications are changing the natural history of this disease, resulting in fewer hospitalizations and operations. In patients with extensive stricturing or numerous previous operations (or both), bowel-sparing techniques such as stricturoplasty may be used (Figure 15.2). In patients with perianal fistulas, a fistulotomy or placement of setons or drains may be used to control symptoms, enhance the effectiveness of medical therapies, and ultimately avoid proctectomy.

Treatment Strategies for Ulcerative Colitis

Induction of Remission

The aminosalicylates are effective for inducing remission in patients with mild to moderate ulcerative colitis. Patients with proctitis alone may be treated with mesalamine suppositories, and those with proctosigmoiditis or left-sided colitis may be treated with mesalamine enemas. Steroid suppositories and enemas can also be used in these situations, although clinical trials and a meta-analysis have shown that mesalamine is superior to steroids.

In patients who do not respond to topical therapy or who cannot administer or tolerate it and in those with pancolonic ulcerative colitis, oral 5-ASA drugs can be used, either alone or in combination with topical therapy. When the choice is between sulfasalazine and the other 5-ASA compounds, the trade-off between cost and side effects needs to be considered. In addition, for patients with significant arthralgias, sulfasalazine may be

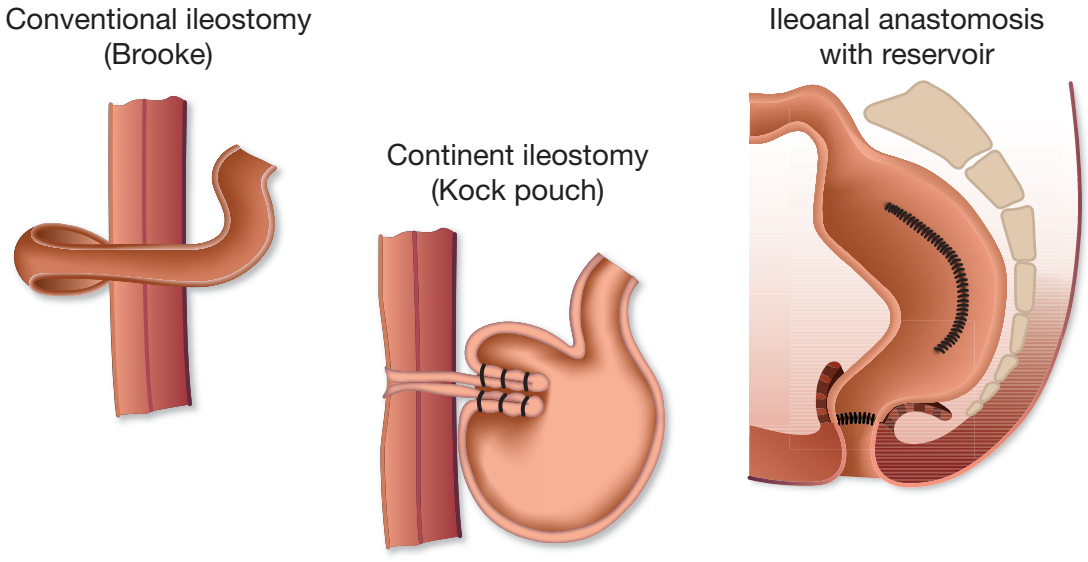

Figure 15.1. Surgical Options for Ulcerative Colitis.

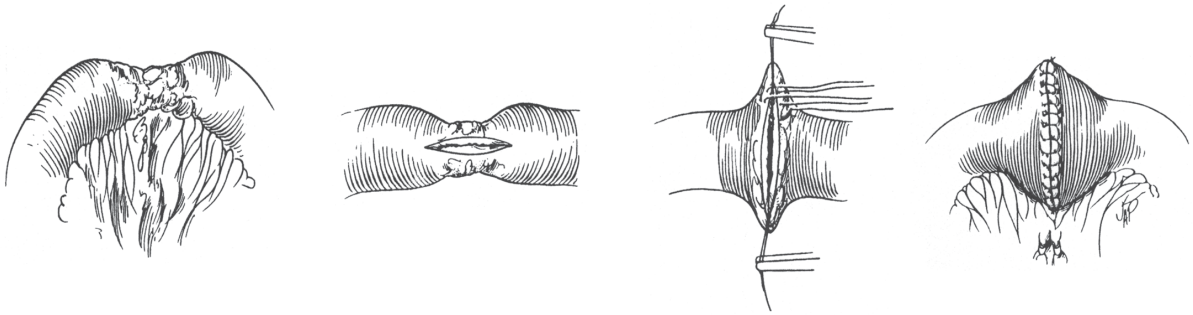

Figure 15.2. **Stricturoplasty for Crohn Disease.**

able to treat the joints and the colitis more effectively than other 5-ASA compounds. In patients treated with a 5-ASA formulation that is pH dependent (Table 15.1), it is important to note that in some patients with active colitis, the colon pH is less than 7; thus, whole pills may pass in their stool. If this happens, an alternative formulation should be used.

For patients with more severe disease and those with moderate disease who do not respond to 5-ASA products, therapy with corticosteroids or an anti-TNF biological is considered. Patients with moderately severe disease can receive oral prednisone or an anti-TNF as an outpatient, while those with fulminant colitis are often hospitalized and treated with intravenous corticosteroids. Patients who respond to corticosteroid therapy require an alternative therapy for maintenance, as discussed below. In those who do not respond, treatment with cyclosporine, an anti-TNF, or colectomy is recommended. Azathioprine or 6-MP can be considered, but usually neither is recommended for induction therapy because the data on efficacy are limited and the onset of action is slow.

Maintenance of Remission

The 5-ASA drugs, including topical therapies in patients with proctitis and proctosigmoiditis, are effective for maintaining remission in ulcerative colitis. Prednisone is not effective for maintaining remission, and patients who respond to this therapy require a steroid-sparing maintenance therapy such as azathioprine or 6-MP. Anti-TNF biologicals are effective for maintaining remission in patients who respond to these agents.

Treatment Strategies for Crohn Disease

Induction of Remission

In 2 older studies, sulfasalazine was modestly effective for inducing remission in patients with active Crohn colitis and ileocolitis, although a recent meta-analysis indicated that the effect size is small. Antibiotics and mesalamine are not consistently effective for inducing remission. Ileal-release budesonide is more effective than mesalamine and is as effective as prednisone (but with fewer side effects) in patients with ileocolonic disease. The colonic-release formulation of budesonide might be considered for induction of colonic Crohn disease.

For patients who have moderate to severe disease and for patients for whom budesonide or sulfasalazine therapy failed, therapy with prednisone or an anti-TNF biological agent might be considered next. Because of the slow onset of action, azathioprine and 6-MP are of limited use as induction agents in patients with significantly active Crohn disease. Methotrexate is sometimes considered as an induction agent in these patients. Natalizumab is restricted to use in patients with significantly active disease who are seronegative for JC polyomavirus and have no response to other therapies.

Special Considerations

Combination Therapy

In the pivotal trials of anti-TNF therapy in Crohn disease, outcomes were no better for patients who were receiving an immunomodulator than for those who were not. However, these were all post hoc, uncontrolled observations and therefore not definitive conclusions. The SONIC trial (Study of Biologic and Immunomodulator Naive Patients in Crohn Disease) compared azathioprine monotherapy, infliximab monotherapy, and combination therapy with both agents in patients with Crohn disease who were naive to both. The efficacy results showed that infliximab was superior to azathioprine and that combination therapy was superior to either treatment alone. In addition, the risk of serious side effects was not increased in the combination arm. Although the SONIC trial assessed infliximab, the same results would probably be seen with the other anti-TNF agents. These data, together with several other lines of evidence showing benefits of combination therapy (eg, better efficacy, fewer anti-therapeutic antibodies) has led to the recommendation to use combination therapy more often in patients with Crohn disease. Similar data are emerging for ulcerative colitis, although they are less clear at the present time.

Top-Down Versus Step-Up

Another topic that is still debated among experts is the administration of anti-TNF biologicals earlier in the course of Crohn disease. Several lines of evidence support this thinking, including the "top-down or step-up" study. Although the design of this study was not ideal with respect to current practice paradigms, it did support the notion that early use of anti-TNF therapy led to better outcomes than the traditional approach of steroids followed by immunomodulators and only then anti-TNF agents. Other evidence supporting the earlier use of anti-TNFs includes data from children and adults that show high response and remission rates when treatment is started earlier in the course of the disease. However, these data would need to be balanced against the cost of currently available anti-TNF drugs. The overall cost of therapy for a patient who responds to steroids and is maintained on an immunomodulator would be considerably less than long-term anti-TNF therapy.

Maintenance of Medically Induced Remission

The 5-ASA drugs and prednisone are not effective for maintenance of medically induced remission. Budesonide prolongs the time to relapse, but a maintenance effect beyond 6 months has not been shown. Azathioprine, 6-MP, methotrexate, anti-TNF agents, and natalizumab are all effective for maintaining remission. Figure 15.3 shows a treatment algorithm for maintenance

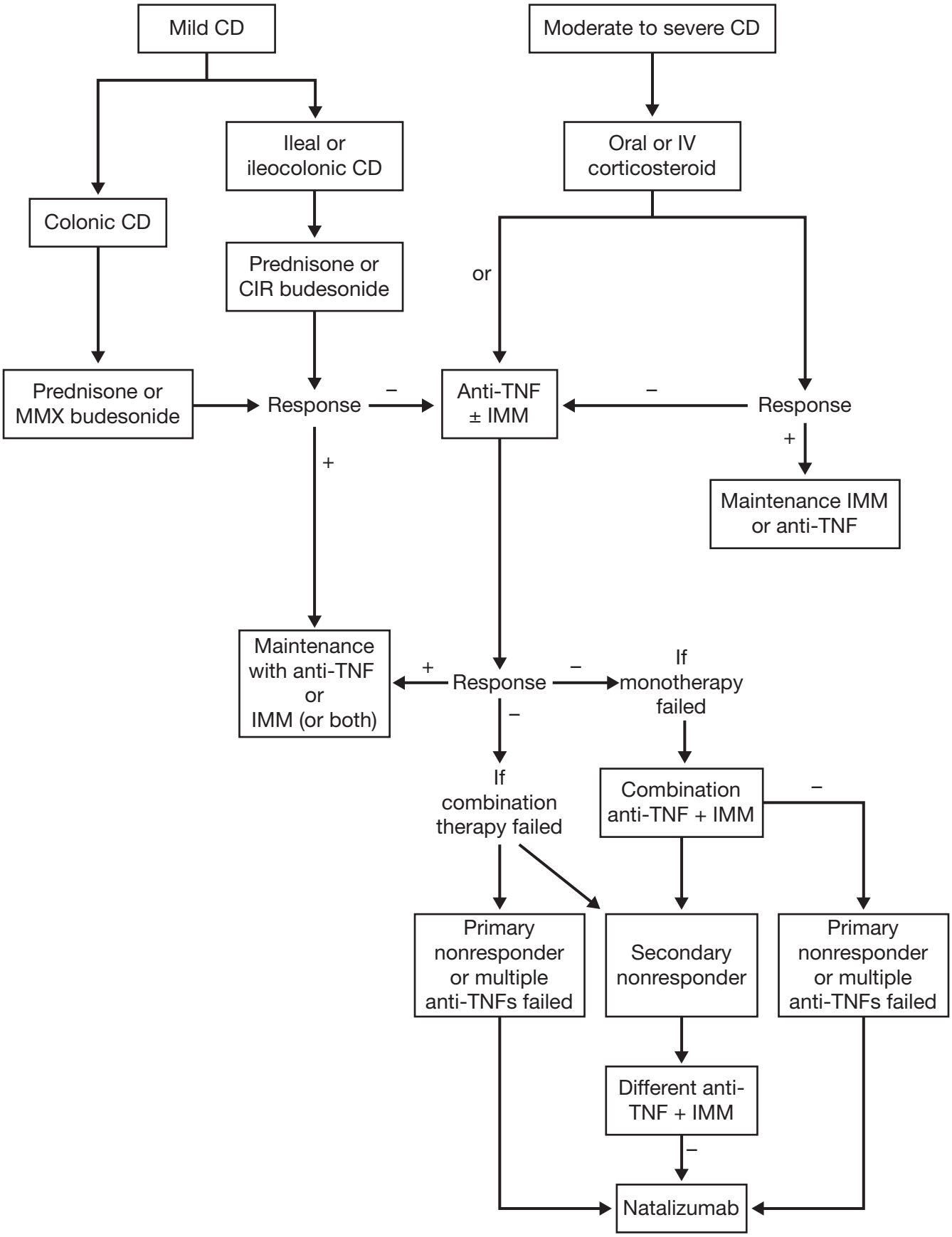

Figure 15.3. Treatment Algorithm for Patients With Crohn Disease (CD). CIR indicates controlled ileal-release; IMM, immunomodulator; IV, intravenous; MMX, multimatrix system (colonic-release formulation); TNF, tumor necrosis factor.

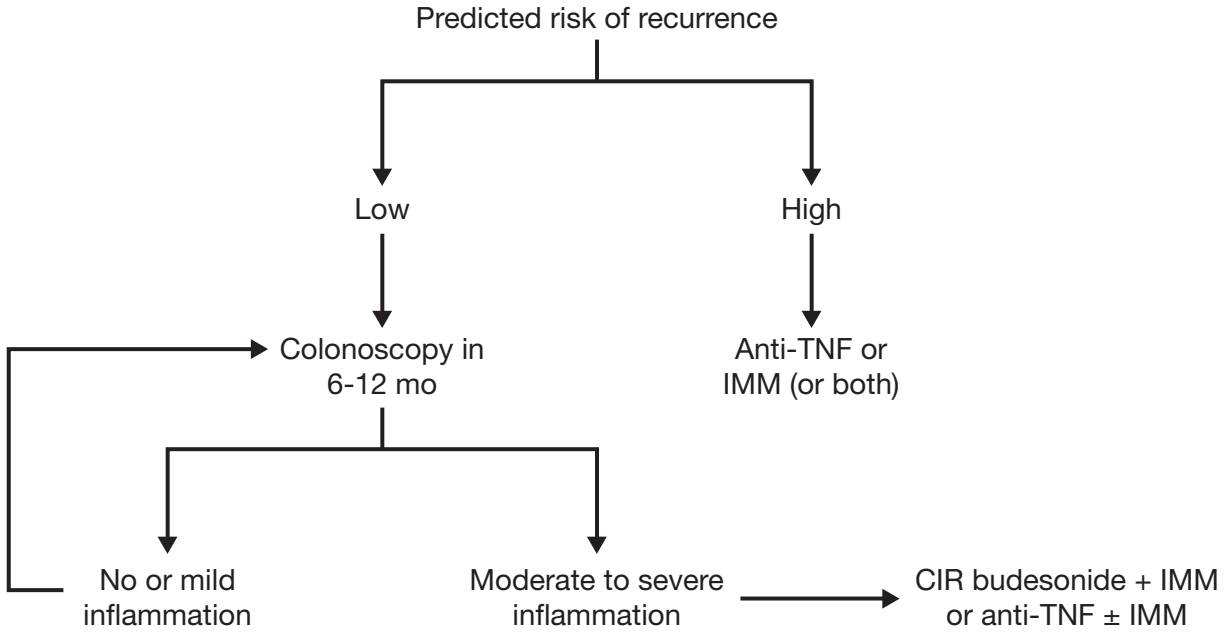

Figure 15.4. **Treatment Algorithm for Postoperative Crohn Disease.** CIR indicates controlled ileal-release; IMM, immunomodulator; TNF, tumor necrosis factor. (Adapted from Sandborn WJ. Medical therapy for Crohn's disease. In: Sartor RB, Sandborn WJ, editors. Kirsner's inflammatory bowel disease. 6th ed. Edinburgh: Saunders; 2004. p. 531-54. Used with permission.)

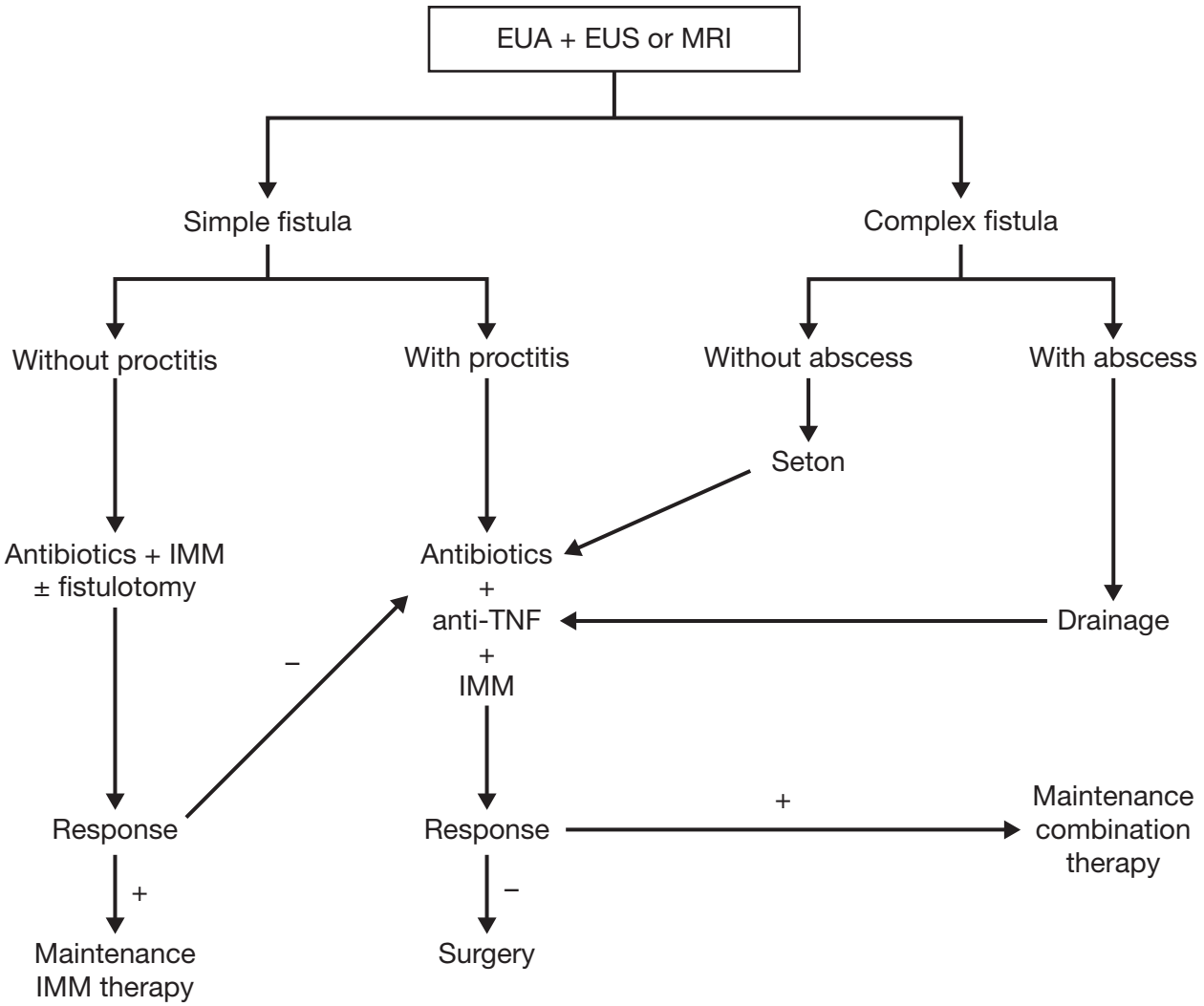

Figure 15.5. **Treatment Algorithm for Perianal Crohn Disease.** EUA indicates examination under anesthesia; EUS, endoscopic ultrasonography; IMM, immunomodulator; MRI, magnetic resonance imaging of the pelvis; TNF, tumor necrosis factor. (Adapted from Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB; American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. Gastroenterology. 2003 Nov;125[5]:1508-30. Used with permission.)

therapy in patients with Crohn disease that is budesonide- or prednisone-dependent or refractory.

Postoperative Maintenance of Remission

No medication has shown benefit for maintaining a surgically induced remission. The 5-ASA drugs are of minimal benefit in this clinical setting. Metronidazole and ornidazole have had some efficacy in small studies, but adverse events are common. A pilot study of ciprofloxacin was negative. Azathioprine and 6-MP may be effective, but data are sparse and conflicting. A small study of infliximab has suggested a possible large benefit for postoperative maintenance of remission, and a large randomized trial is underway to properly assess this question. The current approach to postoperative maintenance therapy is risk stratification of patients for the likelihood of significant postoperative recurrence. Those deemed to be at high risk are offered treatment with azathioprine, 6-MP, or infliximab. Patients not considered to be at high risk, and those who opt not to receive medical therapy, are offered a colonoscopy 9 to 12 months after surgery. Patients who show evidence of significant endoscopic recurrence are then offered treatment. A treatment algorithm for postoperative maintenance therapy for patients with Crohn disease is shown in Figure 15.4.

Treatment of Perianal Crohn Disease

Perianal fistulas can be divided into simple and complex fistulas. A *simple fistula* is below the sphincter complex, has a single external opening, and does not have an associated abscess, rectovaginal fistula, anorectal stricture, or macroscopically evident rectal inflammation. A *complex fistula* is high or has multiple external openings, a perianal abscess, rectovaginal fistula, anorectal stricture, or macroscopic evidence of rectal inflammation.

Antibiotics may be effective for fistula closure, especially for a simple fistula, but no placebo-controlled trial has been performed and the risk of recurrence is high after discontinuation if no other therapy is used. Similarly, azathioprine and 6-MP may be effective for perianal disease, but no controlled trials with fistula closure as the primary end point have been conducted. However, uncontrolled studies, post hoc analyses, and clinical experience have suggested that these treatments may be effective. Anti-TNF agents and natalizumab appear to be effective for both inducing and maintaining fistula closure, although only infliximab has been assessed in randomized trials with fistula closure as the primary end point. An algorithm for the treatment of perianal Crohn disease is shown in Figure 15.5.

Conclusions

There are multiple treatment options for Crohn disease and ulcerative colitis. Many of the drugs can be used for either condition, although some are used for only one or the other. Knowledge of the individual drugs and their characteristics with regard to whether the drug treats systemic disease or local disease, and where in the gastrointestinal tract it releases active drug, is critical for successful treatment of patients with IBD.

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16

Inflammatory Bowel Disease: Extraintestinal Manifestations and Colorectal Cancer

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Ulcerative colitis (UC) and Crohn disease (CD) are inflammatory disorders that affect the gastrointestinal tract. However, these diseases are systemic disorders that may involve other organ systems. Extraintestinal manifestations can affect any organ system, and while in many cases these symptoms are believed to be a result of the underlying intestinal inflammation, some extraintestinal manifestations are independent of the luminal disease course. Extraintestinal manifestations may precede the diagnosis of inflammatory bowel disease (IBD). Many patients experiencing extraintestinal manifestations have colonic disease, and in individuals with 1 extraintestinal manifestation, another extraintestinal symptom is more likely to develop.

This chapter reviews the most common extraintestinal manifestations, their relation to luminal disease activity, and their treatment. Patients with IBD with colonic involvement (UC or CD involving the colon) are at increased risk of colorectal cancer. This chapter also reviews risk factors associated with colorectal cancer and provides guidelines for surveillance measures.

Musculoskeletal Manifestations

Musculoskeletal symptoms (pain) are the most common extraintestinal manifestations of IBD, affecting up to 53% of IBD patients (Box 16.1). Arthritis can affect the spine, the sacroiliac joints, or the peripheral joints. Peripheral and axial arthritis can precede the diagnosis of IBD by many years. IBD arthropathies are seronegative (negative for rheumatoid factor). The prevalence of peripheral and axial arthritis is similar in CD and UC (5%-20%). However, inflammatory joint disease is more common in patients who have CD with colonic involvement than in patients who have other CD phenotypes. IBD arthropathy also appears to be less common in patients with ulcerative proctitis.

Peripheral Arthritis

Patients with peripheral arthropathy experience pain, increased local temperature, joint swelling, and stiffness. These patients generally experience joint stiffness that improves with activity; this feature helps to differentiate IBD-associated arthropathy from osteoarthritis. Plain radiographs of involved joints typically do not show destructive changes. Peripheral arthritis associated with IBD is divided into 2 subtypes.

Type 1 peripheral arthritis is pauciarticular, involving fewer than 5 joints. Larger joints are generally involved, and knees are the most commonly involved joints. This arthritis is associated with disease activity, generally in parallel with the severity of the luminal symptoms, and is also associated with other extraintestinal manifestations. Type 1 peripheral arthritis is self-limited and typically resolves within 1 to 2 months or as the bowel symptoms resolve.

Patients with type 2 peripheral arthritis have a polyarticular arthritis (affecting >5 joints) that is independent of IBD activity. The severity of type 2 peripheral arthritis is also independent of IBD severity. Smaller joints, such as metacarpophalangeal joints, are typically involved, and generally there is symmetrical distribution. This is a chronic arthritis that can last years. Type 2 peripheral arthritis may be associated with uveitis, but it is not associated with other extraintestinal manifestations.

Abbreviations: CD, Crohn disease; COX-2, cyclooxygenase 2; CRC, colorectal cancer; DEXA, dual energy x-ray absorptiometry; EN, erythema nodosum; IBD, inflammatory bowel disease; NSAID, nonsteroidal antiinflammatory drug; pANCA, perinuclear antineutrophil cytoplasmic autoantibody; PG, pyoderma gangrenosum; PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor; UC, ulcerative colitis; UDCA, ursodeoxycholic acid

Box 16.1. Bone and Joint Manifestations of Inflammatory Bowel Disease

Spondyloarthropathy

- Axial skeleton
  - Sacroiliitis
  - Ankylosing spondylitis
- Peripheral
  - Type 1 (oligoarticular)
  - Type 2 (polyarticular) (rare)

Metabolic bone diseases

- Osteoporosis or osteopenia
- Osteomalacia (rare)
- Osteonecrosis (rare)

Treatment of type 1 peripheral arthritis is generally aimed at treating the underlying bowel disease. Nonsteroidal antiinflammatory drugs (NSAIDs) may provide symptomatic relief, although they are not commonly used because of the risk of flaring bowel inflammation. Alternatively, cyclooxygenase 2 (COX-2) inhibitors may provide symptomatic relief and are less likely to worsen underlying IBD. Sulfasalazine, with its antiarthritic sulfapyridine moiety, may provide some relief of arthritic symptoms. Methotrexate has also been used for the treatment of IBD-associated arthropathy. A short course of corticosteroids can be considered for more immediate relief. In refractory cases, tumor necrosis factor (TNF) antagonists may help relieve symptoms of peripheral arthritis.

Axial Arthropathies

Axial arthritis is also associated with IBD but is independent of IBD disease activity. Sacroiliitis, which is often asymptomatic, is more common than ankylosing spondylitis, which is present in only 1% to 6% of patients with IBD. Men tend to be affected more commonly than women although less than previously believed. More recent studies show a 2:1 to 3:1 male to female ratio, compared with earlier studies that showed a 5:1 to 6:1 ratio.

Axial joint disease should be suspected if patients have inflammatory back pain. Inflammatory back pain is a clinical diagnosis based on a history of back pain of insidious onset before the age of 40 to 45 years, pain with stiffness that improves with exercise, pain that is not relieved with rest, and pain that has been present for at least 3 months. Axial arthritis is typically classified as sacroiliitis or ankylosing spondylitis. Sacroiliitis is the more common and often remains undiagnosed. The majority of the patients are asymptomatic. Sacroiliitis is detected in 24% of asymptomatic IBD patients who undergo magnetic resonance imaging. In a subset of patients with sacroiliitis, the disease progresses and ankylosing spondylitis develops. Patients with sacroiliitis who are HLA-B27 positive have a greater risk of progression to ankylosing spondylitis. Sacroiliitis, spinal inflammation, and enthesitis are the characteristic features of ankylosing spondylitis. Progressive ankylosing spondylitis is measured by the presence of new bone formation (syndesmophytes) and ankylosis of the sacroiliac joints and vertebral column. Patients with ankylosing spondylitis may experience limited spinal mobility and decreased chest expansion.

Treatment of sacroiliitis is guided by the patient's symptoms. Asymptomatic patients who have normal spinal mobility and who are HLA-B27 negative do not need specific therapy. However, symptomatic patients should be referred to a physical therapist and monitored for disease progression. First-line treatment for ankylosing spondylitis is physical therapy and use of NSAIDs, which have been shown to prevent radiographic progression of disease. COX-2 inhibitors are the preferred NSAID because they carry a lower risk of exacerbating underlying IBD.

Treatment of ankylosing spondylitis has improved dramatically over recent years with the introduction of TNF antagonists. TNF antagonists have been shown to induce remission, particularly in the earlier stages of ankylosing spondylitis; therefore, TNF antagonists are preferred when NSAIDs have failed. The opportunity to treat and prevent disease progression highlights the importance of early detection of ankylosing spondylitis.

Osteoporosis

Osteoporosis is fairly common in patients with IBD, with a prevalence rate of 15%. The overall fracture risk in IBD patients is 40% higher than in the general population. Common risk factors in this patient population include frequent use of corticosteroids, decreased physical activity, inflammation leading to increased cytokine release (interleukin 1, interleukin 6, and TNF-α) and thereby contributing to bone resorption, malabsorption of calcium and magnesium, vitamin D deficiency, and ileal resorption. Patients who have been treated with corticosteroids for more than 3 months or who have had recurrent courses of corticosteroids should be screened for osteoporosis. The diagnostic standard for bone density measurement is dual energy x-ray absorptiometry (DEXA). Patients who have a low-trauma or fragility fracture or hypogonadism, postmenopausal women, and men older than 50 years should also undergo a DEXA scan.

Dermatologic Manifestations

Dermatologic manifestations are present in 10% of patients when IBD is diagnosed (Box 16.2). The incidence of skin conditions increases over time among patients with CD and UC. The most common dermatologic manifestations of IBD are erythema nodosum (EN), pyoderma gangrenosum (PG), and oral ulcerations. Metastatic CD and Sweet syndrome are less commonly associated with IBD.

EN is the most common cutaneous lesion in IBD patients. It occurs as deep, tender nodules on the extensor surfaces of the

Box 16.2. Dermatologic Manifestations of Inflammatory Bowel Disease

Common

- Pyoderma gangrenosum
- Erythema nodosum
- Cutaneous ("metastatic") Crohn disease
- Aphthous stomatitis

Less common

- Bowel-associated dermatosis-arthritis syndrome (bowel bypass syndrome)
- Sweet syndrome (acute neutrophilic dermatosis)
- Epidermolysis bullosa acquisita
- Mucosal cobblestoning of buccal mucosa and palate
- Pyostomatitis vegetans

lower extremities, although these lesions can also occur on the arms and trunk. EN typically parallels bowel disease activity, and treatment is directed toward the underlying IBD. In severe or refractory cases, corticosteroids can be helpful. EN is associated with conditions other than IBD, including Behçet syndrome and sarcoidosis. EN has also been described in patients with various infections, including *Yersinia* infection, tuberculosis, coccidioidomycosis, histoplasmosis, and blastomycosis.

PG is a painful, ulcerating skin disorder that typically manifests initially as a pustule, papule, or nodule that eventually breaks down into an ulcer with violaceous, undermined borders. These lesions are most commonly encountered on the lower extremities or peristomal region, but because this skin condition is pathergic (similar to Behçet syndrome), these lesions can occur in any area that is frequently traumatized (Figure 16.1). PG may or may not parallel disease activity. Because PG may be associated with active IBD, it is important to treat any underlying bowel inflammation when managing this condition. In addition to treatment for active IBD, patients generally require a taper of high-dose steroids. Topical tacrolimus can also be very helpful in treating these lesions. Milder cases can be managed with dapsone. Despite these measures, PG can be extremely difficult to treat. Other treatments that can be considered for difficult-to-treat lesions include cyclosporine, tacrolimus, azathioprine, and anti–TNF-α agents. Surgical measures should be avoided because of the risk of exacerbating the lesion or inducing new lesions from pathergy.

Oral lesions (aphthous stomatitis) are fairly common in IBD patients, affecting 10% of patients with UC and 20% to 30% of patients with CD. Typical lesions are indistinguishable from canker sores, and often these lesions resolve when the underlying IBD is treated (Figure 16.2). Treatment is symptomatic. Topical anesthetics may be helpful. In some instances, a topical steroid can be applied for more immediate relief.

Metastatic CD is a rare skin manifestation of IBD that is characterized by ulcerating nodules typically present on the anterior abdominal wall, submammary area, arms, legs, or perianal region. Biopsy specimens from these lesions show noncaseating granulomas. The lesions may or may not parallel luminal activity. If luminal activity is present, treatment of the underlying IBD is generally helpful. Corticosteroids and immunosuppressives may also help alleviate these lesions. Case reports have described successful treatment of metastatic CD with metronidazole.

Sweet syndrome, also associated with IBD, occurs as raised, tender nodules on the face, arms, or trunk (Figure 16.3). Patients also exhibit constitutional symptoms, including fever. Biopsy specimens from these lesions show intense neutrophilic infiltrates without underlying vasculitis. Treatment includes corticosteroids and treatment of the underlying IBD.

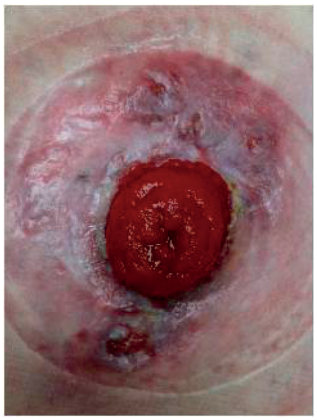

Figure 16.1. Pyoderma Gangrenosum Involving Peristomal Skin.

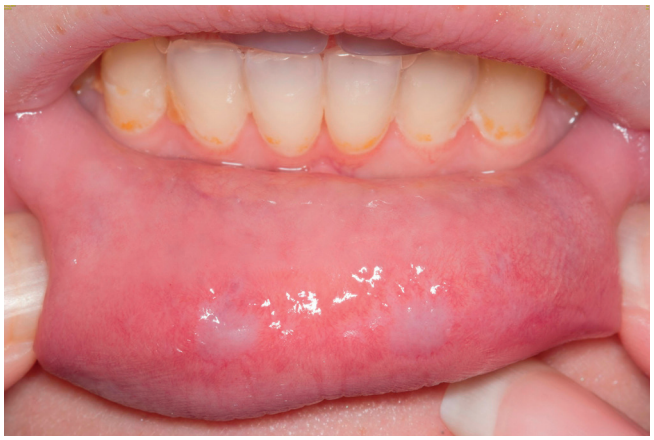

Figure 16.2. Aphthous Ulcers of the Lower Lip.

Ocular Manifestations

Ocular manifestations of IBD are present in up to 5% of patients (Box 16.3). Most patients with ocular symptoms have colonic involvement of IBD. Episcleritis is the most common ocular complication and parallels IBD activity. Patients with episcleritis present with acute redness in 1 or both eyes and a sensation of irritation or burning of the eye. No change in vision is associated with this ocular manifestation. Episcleritis generally resolves with treatment of the underlying bowel disease, although topical steroids can be helpful.

Scleritis, a more severe ocular manifestation, may impair vision and warrants immediate evaluation by an ophthalmologist. The clinical presentation of scleritis is very similar to episcleritis; therefore, it is reasonable to refer all IBD patients with ocular complaints to an ophthalmologist for evaluation. Treatment is aimed at controlling the underlying bowel disease, but oral and topical steroids are often required.

Anterior uveitis (iritis) is associated with other extraintestinal manifestations, including peripheral and axial arthritis and dermatologic manifestations (particularly EN). Approximately 50% of patients with the acute form of uveitis are HLA-B27 positive.

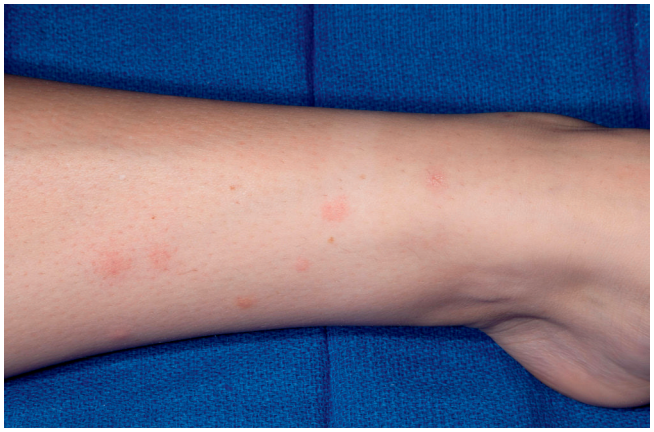

Figure 16.3. Sweet Syndrome Involving the Lower Extremity.

Box 16.3. Ocular Manifestations of Inflammatory Bowel Disease

Inflammatory
- Anterior uveitis (iritis)
- Scleritis
- Episcleritis
- Retinitis (rare)

Treatment-related (corticosteroids)
- Cataracts
- Glaucoma

In these patients, uveitis does not always parallel disease activity. It is associated with eye pain, redness, visual blurring, photophobia, and headaches. This condition should also prompt a referral to an ophthalmologist since untreated uveitis can lead to complications such as cataracts or glaucoma. Characteristic findings on examination include a ciliary flush (intense redness in the center of the eye which lessens in intensity peripherally). Slit-lamp examination shows corneal clouding and conjunctival injection. Treatment consists of oral and topical corticosteroids. Anti–TNF-α agents have been used for refractory cases.

Ocular complications may also develop from medical therapy for IBD. Prolonged courses of corticosteroids can lead to the development of cataracts and glaucoma. Patients who have received long courses of corticosteroids should undergo regular examinations by an ophthalmologist.

Hepatobiliary and Pancreatic Manifestations

The most common hepatobiliary manifestation of IBD is primary sclerosing cholangitis (PSC) (Box 16.4). PSC is an idiopathic, chronic inflammatory disorder of the biliary tree. The inflammatory process can result in stricturing and fibrosis of the medium-sized and large intrahepatic and extrahepatic bile ducts, which leads to the classic "beads-on-a-string" finding on endoscopic or magnetic resonance cholangiography. A strong association exists between PSC and IBD. Although only 2% to 7% of patients with UC have PSC, up to 80% of patients with PSC have IBD, most commonly UC. Patients often have mild pancolitis, although patients with PSC-associated colitis may also have rectal sparing or predominately right-sided colitis with backwash ileitis. This pattern of inflammation likely represents a unique PSC phenotype of IBD. The majority of patients (approximately 80%) have positive test results for perinuclear antineutrophil cytoplasmic autoantibody (pANCA).

Box 16.4. Hepatobiliary Manifestations of Inflammatory Bowel Disease

Biliary
- Primary sclerosing cholangitis (large duct)
- Small duct primary sclerosing cholangitis (formerly known as pericholangitis)
- Cholelithiasis or choledocholithiasis
- Cholangiocarcinoma (rare)
- Primary biliary cirrhosis (rare)

Hepatic
- Fatty liver or steatohepatitis
- Autoimmune hepatitis
- Drug-induced liver injury (thiopurines, methotrexate, 5-aminosalicylates)

PSC is often diagnosed after the onset of IBD, although PSC may develop years before the onset of bowel symptoms. The disease course of PSC is independent of IBD activity. PSC is typically a progressive disease leading to end-stage liver disease. The median survival time after diagnosis is 12 years. Patients with advanced disease may present with pruritus or jaundice. Earlier in the disease course, patients may be asymptomatic and present with findings of mildly abnormal levels of liver enzymes. Any patient with IBD and evidence of cholestasis (elevated alkaline phosphatase level) warrants further evaluation to exclude a diagnosis of PSC. Patients with PSC have an increased risk of cholangiocarcinoma, even in the absence of cirrhosis. The risk of colorectal cancer is also increased in this patient population, so annual surveillance colonoscopies are recommended.

There are no effective medical therapies for PSC. Therapeutic trials of ursodeoxycholic acid (UDCA) have yielded inconsistent results. High dosages of UDCA (25-30 mg/kg daily) may actually be harmful and should be avoided. Liver transplant is often an effective treatment for PSC, although PSC can recur after transplant.

Although rare, autoimmune hepatitis is associated with IBD. An overlap syndrome of autoimmune hepatitis and PSC is also recognized. The serologic findings are characteristic of autoimmune hepatitis (elevated levels of antinuclear antibodies, smooth muscle antibodies, and IgG), and the cholangiographic findings are typical of PSC.

Cholelithiasis is more common in patients with IBD than in the general population. Patients with ileal CD (active inflammation of the terminal ileum or resection of the ileum) are at particular risk for cholelithiasis due to interruption of enterohepatic cycling of bile salts leading to disruption of the processing of cholesterol and phospholipids. These patients may form cholesterol stones.

Pancreatitis is also seen in patients with IBD. Pancreatitis is a fairly common side effect of thiopurine therapy and a less common side effect of 5-aminosalicylic acid or corticosteroid therapy. In patients with CD involving the duodenum, pancreatitis may develop from active disease disrupting the drainage of pancreatic juices into the bowel. In patients with CD, a granulomatous inflammatory process can involve the pancreas.

Miscellaneous Complications

Patients with IBD may have various miscellaneous extraintestinal manifestations and complications (Box 16.5).

Nephrolithiasis is a recognized problem for patients with CD, particularly ileal CD. Disease or resection of the terminal ileum leads to bile salt malabsorption, and, in cases of extensive disease or resection, fat malabsorption. In patients with fat malabsorption, free calcium binds to fatty acids rather than oxalate within the intestinal lumen. The oxalate is then absorbed, leading to increased urinary oxalate excretion and a risk of calcium oxalate stone formation. In patients who have less extensive involvement of the terminal ileum and subsequent bile salt malabsorption, increased colonic permeability to small molecules develops from the exposure of the bile salts to the colonic epithelium. This increased permeability leads to absorption of oxalate and increased urinary oxalate excretion. In patients with IBD,

Box 16.5. Miscellaneous Extraintestinal Manifestations and Complications of Inflammatory Bowel Disease

Renal
- Nephrolithiasis (oxalate, urate)
- Glomerulonephritis (rare)
- Right ureteral obstruction
- Urinary system fistulas (eg, enterovesical, colovesical, rectourethral)
- Tubulointerstitial nephritis (5-aminosalicylates)
- Secondary amyloidosis

Hematologic
- Anemia
  - Iron deficiency
  - Vitamin B_{12} deficiency
  - Folic acid deficiency
  - Anemia of chronic disease
  - Autoimmune hemolytic anemia
- Neoplastic
  - Myelodysplastic syndrome (rare)
  - Promyelocytic leukemia (rare)

Cardiopulmonary
- Pericarditis (extraintestinal manifestation or drug-induced)
- Myocarditis
- Conduction abnormalities
- Pneumonitis
- Eosinophilic pneumonia
- Cryptogenic organizing pneumonia
- Bronchiectasis, bronchiolitis, bronchitis, and subglottic stenosis

Pancreatic
- Acute pancreatitis
  - Drug-induced (purine analogues, 5-aminosalicylates)
  - Duodenal Crohn disease
  - Granulomatous involvement of pancreas (rare)
- Chronic pancreatitis
  - Autoimmune pancreatitis

Thrombophilia
- Multifactorial

uric acid stones may also develop as a result of hypovolemia and metabolic acidosis from diarrhea.

Secondary amyloidosis is a rare complication of many inflammatory diseases, including IBD. This complication more commonly affects patients with CD rather than UC. Patients may present with proteinuria or renal failure. Treatment is aimed at the underlying bowel disease, but in some instances, renal transplant may improve survival.

Patients receiving 5-aminosalicylate therapy should be monitored for interstitial nephritis, a rare idiosyncratic reaction to this class of medication. Renal function should be monitored on a regular basis in these patients.

Thromboembolism is also a complication of IBD. Compared with the general population, IBD patients have a 3-fold risk of deep vein thrombosis or pulmonary embolism. IBD is a risk factor for venous thromboembolism, whereas neither rheumatoid arthritis nor celiac disease increases the risk of thromboembolism. One-third of IBD patients with a venous thromboembolism have no risk factors for thromboembolism except a diagnosis of IBD. Thromboembolic events are most common in patients with active disease but can also occur in patients with disease in partial or full remission. Prevention is of utmost importance. All acquired risk factors for thrombosis should be addressed with any patient who has IBD. Effective treatment of luminal disease, maintenance of hydration, mobilization, treatment of vitamin deficiencies (folate, vitamins B_{12} and B_6), and prophylaxis for high-risk patients should be instituted. The American College of Chest Physicians recommends pharmacologic prophylaxis for any acutely ill hospitalized IBD patient. Sequential compression devices should be used only if pharmacologic prophylaxis is contraindicated.

Colorectal Cancer

Patients with IBD involving the colon have an increased risk of colorectal cancer (CRC) compared with the general population (Box 16.6). This risk increases as the duration of disease increases, with an estimated incidence rate of 18% after 30 years of disease in patients with UC. Methods to identify patients at greatest risk of CRC development are imperfect. The current standard surveillance program includes multiple random biopsies obtained throughout the colon at regularly scheduled intervals. This approach has been the preferred method of surveillance for the past 30 years. Chromoendoscopy is also an effective surveillance tool in the IBD population, but it is tedious and time consuming, and it is not performed by most endoscopists. Furthermore, the benefit of chromoendoscopy compared with targeted biopsies using high-definition colonoscopes has yet to be determined. As technology advances, strategies to detect neoplasia in patients with long-standing colitis will continue to evolve.

The risk of CRC increases with the extent of disease and disease duration. Generally, initiation of surveillance colonoscopies should begin 8 to 10 years after diagnosis. Patients with disease limited to the rectum do not have an increased risk of CRC and do not need to undergo surveillance colonoscopies. A minimum of 32 biopsies should be obtained throughout the colon, and many experts advocate 4-quadrant biopsies every 10 cm, with targeted biopsies of suspicious lesions.

The recommendations for interval surveillance colonoscopies vary among professional societies. There is agreement that patients with the highest risk of CRC (eg, patients with PSC or prior dysplasia) should undergo annual colonoscopies. The American Gastroenterological Association recommends colonoscopy every 1 to 3 years, with more frequent colonoscopies for patients at higher risk.

Box 16.6. Risk Factors for Colorectal Cancer in Inflammatory Bowel Disease
- Extent of colitis
- Duration of disease
- Family history of colorectal cancer
- Primary sclerosing cholangitis
- Medical nonadherence or lack of follow-up
- No use or minimal use of sulfasalazine or 5-aminosalicylates

Surveillance guidelines were developed with UC patients in mind. However, patients with CD involving the colon also have an increased risk of neoplasia. Risk factors for neoplasia include younger age at diagnosis, longer disease course, and greater intervals between colonoscopies. For all practical purposes, patients with CD involving more than one-third of the colon are considered to have a CRC risk that is similar to the risk for patients with UC.

Patients who have flat, high-grade dysplasia have a high risk of synchronous cancer and a great risk of receiving a CRC diagnosis at a subsequent examination. Given the high risk of CRC among these patients, colectomy is the standard of care. There is some debate on the most appropriate management of patients with flat, low-grade dysplasia. Colectomy is often offered to these patients as well, but in some cases, patients are monitored closely with surveillance colonoscopies every 3 to 6 months with or without chromoendoscopy. The management of polypoid dysplasia also varies among practicing physicians. In the absence of flat dysplasia in the mucosa surrounding the lesion, polypoid lesions may be removed endoscopically with close follow-up.

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17

Gastrointestinal Infections, *Clostridium difficile*–Associated Disease, and Diverticular Disease[a]

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Infections are a common cause of gastrointestinal tract disease. This chapter focuses on the more common infectious causes of diarrhea, food poisoning, and diverticulitis. It does not review *Helicobacter pylori* infection, small intestinal bacterial overgrowth, or infections in patients seropositive for human immunodeficiency virus (HIV), because those topics are considered in other chapters.

Worldwide, an estimated 1 billion cases of infectious diarrhea occur annually, and the death rates are second only to those of cardiovascular disease. It is estimated that every 10 seconds worldwide, infectious diarrhea causes the death of 1 child younger than 5 years. Thus, in some areas, diarrheal diseases are responsible for more years of life lost than all other causes combined. Infectious diarrhea is more common in children and in developing countries than in adults in developed countries. In developed countries, the infections are usually mild and self-limited and, thus, antibiotic therapy is unnecessary. In specific cases, antibiotics are not effective (Box 17.1). The clinical features of infectious diarrhea vary, depending on whether the organism is invasive and whether the infection occurs in the small bowel or colon (Table 17.1).

[a] Portions of this chapter were adapted from Yassin SF, Young-Fadok TM, Zein NN, Pardi DS. *Clostridium difficile*: associated diarrhea and colitis. Mayo Clin Proc. 2001 Jul;76(7):725-30. Used with permission of Mayo Foundation for Medical Education and Research

Abbreviations: EAEC, enteroaggregative *Escherichia coli*; EHEC, enterohemorrhagic *Escherichia coli*; EIEC, enteroinvasive *Escherichia coli*; ELISA, enzyme-linked immunosorbent assay; EPEC, enteropathogenic *Escherichia coli*; ETEC, enterotoxigenic *Escherichia coli*; HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; PCR, polymerase chain reaction; TMP-SMX, trimethoprim-sulfamethoxazole; TTP, thrombotic thrombocytopenic purpura

Viruses

In the United States, most cases of gastroenteritis are viral and usually are brief and self-limited (Table 17.2). Viral gastroenteritis usually is characterized by diarrhea of brief duration, often with nausea and vomiting, and by the absence of high fever, severe abdominal pain, and bloody diarrhea. Therapy is symptomatic with antiemetics, antipyretics, and attention to adequate hydration.

Rotavirus

Rotavirus is the most common cause of diarrhea in young children worldwide. Adult infection often occurs after contact with a sick child or as part of an institutional epidemic. In tropical climates, rotavirus infection occurs year-round; in temperate climates, it is more common in the winter. Spread is by the fecal-oral route, facilitated by prolonged survival in the environment and resistance to many disinfectants. Symptoms occur within 72 hours after exposure, last up to 5 days, and include mild fever, diarrhea, and vomiting. Most adults are mildly symptomatic or asymptomatic, but the disease can be severe in persons who are immunocompromised, malnourished, or chronically ill. Death can occur from dehydration and acidosis, usually in the very young or elderly. Symptoms may be prolonged because of transient disaccharidase deficiency caused by damage to small-bowel epithelial cells, with a resultant decrease in brush border enzymes. Treatment focuses on rehydration. Oral rehydration is optimal because oral nutrition stimulates mucosal repair, shortening the duration and lessening the severity of the illness. Protective immunity may not develop after natural infections, although reinfection tends to be less severe. A rotavirus vaccine has been developed and approved for use in infants. In the United States, rotavirus vaccination is now part of the recommended immunization schedule for children up to 6 years old.

Box 17.1. Effectiveness of Antibiotic Therapy for Infectious Diarrhea Caused by Various Agents and Infections

Antibiotics are effective and indicated
- *Salmonella* enterocolitis in an immunocompromised host
- *Salmonella* typhoid fever
- *Shigella*
- *Clostridium difficile*
- *Yersinia* sepsis or systemic infection
- Moderate to severe traveler's diarrhea
- *Campylobacter* dysentery or sepsis
- *Vibrio cholera*
- *Giardia*
- Amebiasis

Antibiotics are possibly effective
- Enteroinvasive *Escherichia coli*
- Enteropathogenic *E coli*
- *Campylobacter enteritis*
- *Vibrio parahaemolyticus*

Antibiotics probably are not effective
- Enterohemorrhagic *E coli* (including O157:H7)
- *Salmonella* enterocolitis
- *Yersinia* enteritis without sepsis
- Mild to moderate traveler's diarrhea

Adapted from Banerjee S, LaMont JT. Treatment of gastrointestinal infections. Gastroenterology. 2000 Feb;118(2 Suppl 1):S48-67. Used with permission.

Caliciviruses

Caliciviruses, also known as small round-structured viruses, are the most important cause of viral gastroenteritis in adults, and they cause many outbreaks in young children and adults. The most common calicivirus is norovirus (also known as Norwalk-like virus). Outbreaks are associated with contaminated food (eg, shellfish) or water or with person-to-person spread. Caliciviruses are common in the environment and are resistant to disinfectants and chlorination. The incubation period is less than 48 hours, followed by illness lasting up to 3 days. Infection occurs in the proximal small bowel. Diarrhea, nausea, vomiting, abdominal pain, fever, headache, and malaise are common but typically mild. Postinfectious immunity is not permanent or fully protective against reinfection.

Astrovirus

Astrovirus is an important cause of diarrhea in infants and children, particularly in developing countries. Nausea and vomiting are less commonly reported than with rotavirus. The incubation period is 2 to 4 days. Illness is mild and lasts up to 5 days.

Enteric Adenovirus

Most adenoviruses cause respiratory infection, although some strains cause diarrhea. Respiratory symptoms may precede gastrointestinal manifestations. A long incubation period (up to 10 days) and diarrhea of long duration (1-2 weeks) are characteristic.

Table 17.1. Clinical Features of Infectious Diarrhea

	Location	
Feature	*Small Bowel*	*Large Bowel*
Pathogens	*Salmonella*	*Campylobacter*
	Vibrio cholerae	*Salmonella*
	Escherichia coli (ETEC, EPEC)	*Shigella*
	Yersinia	*Yersinia*
	Rotavirus	*Escherichia coli* (EIEC, EHEC)
	Norovirus	*Clostridium difficile*
	Adenovirus	*Antamoeba histolytica*
	Giardia	Cytomegalovirus
	Cryptosporidium	
Location of pain	Mid abdomen or diffuse	Lower abdomen, rectum
Volume of stool	Large	Small
Type of stool	Watery	Mucoid, bloody
Fecal leukocytes	Rare	Common
Other	Dehydration, malabsorption	Tenesmus if proctitis

Abbreviations: EHEC, enterohemorrhagic *E coli*; EIEC, enteroinvasive *E coli*; EPEC, enteropathogenic *E coli*; ETEC, enterotoxigenic *E coli*.
Adapted from Hamer DH, Gorbach SL. Infectious diarrhea and bacterial food poisoning. In: Feldman M, Friedman LS, Sleisenger MH, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 2. 7th ed. Philadelphia (PA): WB Saunders Company; c2002. p. 1895. Used with permission.

Bacteria

Bacteria are relatively uncommon causes of acute diarrhea, and the indiscriminate culturing of stool from patients with acute diarrhea produces few positive findings, with an unacceptably high cost per positive culture. However, stool cultures are appropriate for patients who are immunocompromised or who have bloody diarrhea, high fever or pain, fecal leukocytes, or diarrhea persisting longer than a few days. In most laboratories, routine stool cultures detect *Salmonella, Shigella*, and *Campylobacter. Escherichia coli* O157:H7, *Yersinia, Vibrio*, and others often require a special request.

In healthy adults, many bacterial causes of diarrhea do not require antibiotic therapy. However, in those who have bloody stools, high fever, or a chronic illness, including patients who are immunocompromised, empirical antibiotic therapy is often provided while the results of stool culture are pending. Quinolones are usually given for empirical coverage in adults. The more common causes of bacterial diarrhea are summarized in Table 17.3.

Campylobacter

Campylobacter is the most commonly identified bacterial cause of diarrhea in the United States and is twice as common as *Salmonella* and 7-fold more common than *Shigella*. Most

Table 17.2. Summary of Viral Diarrhea

Virus	*Incubation, d*	*Duration, d*
Rotovirus	1-3	4-5
Norovirus	1-2	2-3
Adenovirus	8-10	7-14
Astrovirus	2-4	3-5

Adapted from Czachor JS, Herchline TE. Infectious diarrhea in immunocompetent hosts. Part 1. Bacteria, viruses and parasites. Hosp Physician. 1996;8:10-7. Used with permission.

Table 17.3. Summary of Bacterial Diarrhea

Bacteria	*Incubation, d*	*Duration, d*	*Dysentery (Blood, Mucus)*[a]	*Source*
Salmonella				Chicken, eggs, meat, dairy products
Gastroenteritis	1-2	3-7	0	
Colitis	1-2	14-21	+ to ++	
Typhoid fever	7-14	28	+	
Shigella	1-2	5-7	+++	P-P, egg salad, dairy products
Campylobacter	1-4	5-7	++	Poultry, milk
Escherichia coli O157:H7	3-5	3-8	+++	Hamburger, salami
Vibrio parahaemolyticus	<1-2	2-5	0 to ++	Shellfish
Vibrio cholerae	1-3	4-7	0	Water, shellfish
Yersinia	4-7	7-21	0 to +	Pork, milk

Abbreviation: P-P, person-to-person.
[a] Scale ranges from 0 (absent) to +++ (common).
Adapted from Czachor JS, Herchline TE. Infectious diarrhea in immunocompetent hosts. Part 1. Bacteria, viruses and parasites. Hosp Physician. 1996;8:10-7. Used with permission.

infections are due to *Campylobacter jejuni* and typically are acquired from contaminated poultry (up to 90% of chickens may be colonized) or unpasteurized milk in the summer or early autumn. Infection is most common in very young children, teens, and young adults.

Fevers, myalgias, malaise, abdominal pain, and headache follow an incubation period of 1 to 4 days. Diarrhea begins later and ranges from profuse watery to bloody, lasting up to 1 week. Prolonged carriage can occur for several months, and recurrent infection can occur in up to 25% of patients. A chronic carrier state is rare. Hemolytic uremic syndrome (HUS), reactive arthritis (HLA-B27), and Guillain-Barré syndrome can occur.

In most healthy patients, symptoms are mild to moderate, and by the time the slow-growing *Campylobacter* is identified, the patient's condition has begun to improve. For these patients, antibiotic therapy is unnecessary. Antibiotics are recommended for prolonged (>1 week) or worsening symptoms, dysentery, high fever, bacteremia, pregnant women, and persons at risk for complications (extremes of age, immunocompromised state, or cirrhosis). Quinolones and erythromycin are effective therapy. Erythromycin is less expensive, with less resistance, but treatment must be started early (within the first 3 days of symptoms). Treatment with quinolones can be started later in the illness, but high rates of resistance have been reported.

Salmonella

Infection with *Salmonella* causes a spectrum of diseases ranging from gastroenteritis to typhoid fever (Table 17.4). Infection can be complicated by bacteremia resulting in disseminated infection. *Salmonella typhi* and *Salmonella paratyphi* cause typhoid fever. The other serotypes (about 2,000 have been described) cause nontyphoidal salmonellosis. *Salmonella enteritidis* and *Salmonella typhimurium* are the 2 most commonly isolated serotypes in the United States.

Outbreaks typically occur in the summer or autumn and are associated with contaminated food (undercooked or raw poultry or eggs, meat, or dairy products), reflecting the high colonization rates of *Salmonella* in poultry and livestock. Pets, including turtles, reptiles, cats, and dogs, can carry and transmit the organism. Person-to-person spread is also important in outbreaks and in developing countries. Because typhoidal *Salmonella* exists only in humans, a new case of typhoid fever indicates exposure to a carrier. Attack rates are highest among infants, the elderly, and persons with decreased stomach acid. Conditions that predispose to *Salmonella* infection, in addition to eating raw or undercooked eggs and poultry, are listed in Box 17.2.

Table 17.4. Clinical Syndromes of *Salmonella* Infection

Syndrome	*Incidence, %*
Gastroenteritis	75
Varies from mild to severe (dysentery)	
Bacteremia	5-10
With or without gastroenteritis	
Consider AIDS	
Typhoid (enteric) fever	5-10
With or without gastroenteritis	
Systemic infection	5
Osteomyelitis, arthritis, meningitis, cholecystitis, abscess	
Carrier state duration >1 y	<1

Adapted from Giannella RA. Infectious enteritis and proctocolitis and bacterial food poisoning. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 2. 9th ed. Philadelphia (PA): Saunders/Elsevier; c2010. p. 1843-87. Used with permission.

Gastroenteritis occurs in 75% of infections and typically begins with nausea and vomiting, within 48 hours after exposure, followed by diarrhea and cramps. Diarrhea may range from mild to severe and from watery to bloody. Fever and abdominal pain are common. Localized tenderness can simulate an acute abdomen and is often localized to the right lower quadrant, reflecting the ileal location of most infections. Gastroenteritis usually lasts for no more than 7 days, although in unusual cases, primarily with colitis, symptoms can last for weeks. Bacteremia occurs in 5% to 10% of infections, often resulting in distant infections (eg, central nervous system infections, endocarditis, or osteomyelitis). Recurrent or persistent bacteremia can occur in patients with AIDS.

Typhoid fever (enteric fever) is a systemic infection characterized by an incubation period of 1 to 2 weeks, followed by systemic symptoms that include fever, malaise, arthralgia, myalgia, headache, and delirium. Gastrointestinal symptoms are often delayed and include abdominal pain and constipation more frequently than diarrhea. Delayed bowel perforation and bleeding can occur. Physical examination findings include relative bradycardia (pulse-temperature dissociation), hepatosplenomegaly, lymphadenopathy, and a macular rash (rose spots). Typhoid fever is associated with recurrent or sustained bacteremia, which results in metastatic infections. Symptoms typically last 4 weeks,

Box 17.2. Conditions Predisposing to *Salmonella* Infection

Hemolytic anemia

- Sickle cell disease

Malignancy

- Lymphoma
- Leukemia
- Disseminated carcinoma

Immunosuppression

- AIDS
- Corticosteroids
- Chemotherapy, radiotherapy

Achlorhydria

- Gastric surgery
- Proton pump inhibitors
- Idiopathic

Ulcerative colitis

Schistosomiasis

Adapted from Giannella RA. Infectious enteritis and proctocolitis and bacterial food poisoning. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 2. 9th ed. Philadelphia (PA): Saunders/Elsevier; c2010. p. 1843-87. Used with permission.

although antibiotic therapy can hasten recovery. Recurrent infection, occurring 7 to 10 days after apparent recovery, is not uncommon. The incidence of typhoid fever is decreasing in the United States.

Prolonged asymptomatic fecal shedding of *Salmonella* is common (average duration, about 5 weeks), although most patients clear the organism within 3 months. Chronic carriage (>1 year) occurs in less than 1% of patients with gastroenteritis and in up to 3% with typhoid fever. Risk factors include extremes of age and cholelithiasis (associated with chronic gallbladder infection).

Therapy for uncomplicated gastroenteritis includes rehydration and avoidance of antimotility agents. Antibiotics may prolong the carrier state and select resistant organisms; they do not improve outcomes and are not indicated for healthy patients with uncomplicated gastroenteritis. Antibiotics (eg, quinolones, amoxicillin, and trimethoprim-sulfamethoxazole [TMP-SMX]) are indicated for colitis, for patients with bacteremia or at risk for bacteremia (extremes of age, immunocompromised state [HIV, medications, or malignancy], valvular heart disease, hemoglobinopathy, or orthopedic implants), for severe disease, and for long-term carriers. Multidrug resistance is becoming a problem; therapy should be guided by sensitivity testing. Prolonged therapy is necessary for metastatic infections.

For typhoid fever, therapy is recommended. Typically, quinolones or third-generation cephalosporins are given as empirical therapy while sensitivity data are pending. In cases of fluoroquinolone resistance, azithromycin is the treatment of choice. Resistance to chloramphenicol, TMP-SMX, and ampicillin makes these drugs inappropriate for empirical therapy. Corticosteroids also may be beneficial for patients with severe disease. In long-term carriers, therapy with a quinolone (eg, norfloxacin, 400 mg twice daily for 4 weeks) may lead to clearance. If not, cholecystectomy may be needed to remove the nidus of chronic infection.

Shigella

Shigella has 40 serotypes in 4 species (*Shigella dysenteriae, Shigella flexneri, Shigella boydii*, and *Shigella sonnei*). Spread is typically person to person, facilitated by a low infective dose because of resistance to stomach acid. Outbreaks are related to contaminated food and water. *Shigella sonnei* produces the mildest disease and is the most common type in the United States. Symptoms characteristically begin within 48 hours after ingestion and include fever, malaise, abdominal pain, and watery diarrhea. Rectal pain or burning can be prominent. Respiratory symptoms are common, and children may have neurologic manifestations, including seizures. The diarrhea may decrease and become bloody with mucus and pus (ie, dysentery). This classic progression occurs in a small proportion of cases and is least common for *S sonnei* infections.

The initial watery diarrhea is thought to be due to the Shiga toxin, whereas dysentery is due to mucosal invasion, which occurs primarily in the colon. Bacteremia is uncommon. Predictors of severity include extremes of age, malnutrition, immunocompromise, and infection with *S dysenteriae*. That species is most likely to cause complications such as HUS (see below), dysentery, and toxic megacolon. Shigellosis typically lasts for 1 to 3 days in children and 5 to 7 days in adults. Although chronic carriage is unusual, prolonged infections can occur and be difficult to differentiate from ulcerative colitis. A delayed, asymmetric large-joint arthritis can occur, usually in persons with HLA-B27.

Treatment focuses on rehydration and perhaps avoidance of antimotility agents. Healthy patients whose condition improves spontaneously may not require therapy. However, antibiotics have been shown to decrease mortality and the duration of disease. Therefore, antibiotic therapy is indicated for most patients, particularly those with chronic illnesses (including malnutrition and HIV), the elderly, day care or health care workers, and food handlers. Ciprofloxacin is the treatment of choice (500 mg twice daily for 5 days), with TMP-SMX or azithromycin as an alternative. Resistance to multiple antibiotics has been reported (eg, amoxicillin, ampicillin), and if therapy is begun before sensitivity data are available, quinolones are recommended (for adults). For all patients, hand washing and other hygienic practices are necessary to decrease person-to-person spread and to limit outbreaks.

Escherichia coli

The different types of *E coli* are summarized in Table 17.5.

Enterohemorrhagic *E coli*

Enterohemorrhagic *E coli* (EHEC) produces Shiga toxin and causes colitis after an incubation period of 3 to 5 days. *Escherichia coli* O157:H7 accounts for more than 90% of EHEC cases in the United States; 100 other serotypes have been identified. Although several outbreaks have attracted considerable media attention, most cases of EHEC are sporadic. It has been estimated that 50% of cattle and 90% of hamburger lots are contaminated with EHEC. Thus, EHEC is associated with the ingestion of undercooked hamburger but also with the ingestion of salami, sprouts, and unpasteurized milk or juice. Although the infectious dose is low, EHEC is effectively killed at temperatures higher than 69°C.

Table 17.5. Types of *Escherichia coli* Causing Infectious Diarrhea

Type of E coli	*Patients Affected*	*Pathophysiology*	*Clinical Features*
Enteropathogenic (EPEC)	Infants in developing countries; some travelers	Attachment alters brush border	Watery diarrhea
Enterotoxigenic (ETEC)	Children in developing countries; travelers	Enterotoxin-mediated secretion	Watery diarrhea
Enteroinvasive (EIEC)	All ages; rare; food and water outbreak	Direct invasion	Usually watery diarrhea; 10% have dysentery
Enterohemorrhagic (EHEC) (eg, *E coli* O157:H7)	All ages; food (hamburger); sporadic or outbreak	Shiga-like cytotoxins	Watery then bloody diarrhea; HUS or TTP
Enteroaggregative (EAEC)	Infants in developing countries; HIV-positive adults	Adherence; toxins	Prolonged watery diarrhea

Abbreviations: HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.
Adapted from Giannella RA. Infectious enteritis and proctocolitis and bacterial food poisoning. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 2. 9th ed. Philadelphia (PA): Saunders/Elsevier; c2010. p. 1843-87. Used with permission.

A pink center in a hamburger is associated with lower temperatures and an increased risk of infection. Irradiation of hamburger also effectively kills EHEC, but whether the public will embrace irradiated foods is not known.

EHEC typically produces watery diarrhea that progresses to bloody diarrhea after a few hours to a few days. One study suggested that EHEC is the most common cause of bloody diarrhea in the United States. Systemic symptoms (fatigue, myalgias, and headache), severe abdominal pain, nausea, and vomiting are common, but fever is not. Illness typically lasts 5 to 10 days. In the elderly, EHEC may be misdiagnosed as ischemic colitis.

EHEC can lead to HUS or thrombotic thrombocytopenic purpura (TTP) in 5% of patients, resulting in hemolytic anemia and renal failure, with or without central nervous system symptoms. The pathophysiologic mechanism of EHEC appears to be vascular endothelial damage that leads to platelet aggregation and initiation of the coagulation cascade. This, in turn, leads to ischemia of the colon and results in hemorrhagic colitis. In fact, some cases of "ischemic colitis" probably represent misdiagnosed cases of EHEC. Similar thrombi and ischemia in the kidney may be the cause of renal insufficiency in HUS. HUS or TTP can have high morbidity and mortality rates, particularly among the very young and very old.

In some laboratories, specific testing for *E coli* O157:H7 (sorbitol-MacConkey agar or a newer stool toxin assay that may be more sensitive) must be requested; thus, the condition can be underdiagnosed. In several large series reported from North America, *E coli* O157:H7 was the second to fourth most commonly identified bacterium in acute diarrheal illnesses. Antibiotics do not appear to be beneficial and may increase toxin production or release (or both). This, in turn, may increase the risk of HUS or TTP and, perhaps, death. Also, antimotility agents, including narcotics, may increase the risk of HUS. Thus, antibiotics and antimotility agents should be avoided if EHEC infection is suspected clinically (eg, absence of fever in a patient with bloody diarrhea of suspected infectious origin).

Contact isolation precautions are necessary for patients with EHEC, and any personal contacts who have gastrointestinal tract symptoms should be tested for EHEC. It has been recommended that children, food handlers, and health care workers delay their return to school or work until they are asymptomatic and have had several stool cultures negative for EHEC.

Enterotoxigenic *E coli*

Enterotoxigenic *E coli* (ETEC) is a common cause of diarrhea in travelers and in children in developing countries. The organism attaches to the small bowel and causes diarrhea through enterotoxins. The disease ranges from mild to severe watery diarrhea often associated with mild upper gastrointestinal tract symptoms that last for 2 to 5 days. Rehydration is the mainstay of therapy. Antibiotics (quinolones, TMP-SMX, and rifaximin) often are given empirically for moderate to severe traveler's diarrhea. As with most gastrointestinal infections, multiple drug resistance to antibiotics has been reported with ETEC, although resistance to quinolones does not yet appear to be a major problem.

Enteropathogenic *E coli*

Enteropathogenic *E coli* (EPEC) is primarily a problem in infants. It caused several epidemics with high mortality in neonatal nurseries in the early 1970s. Currently, it occurs most often in developing countries. EPEC attaches to the small-bowel mucosa and causes watery mucoid diarrhea by producing structural changes in the microvilli. Antibiotic therapy is effective, although resistance to TMP-SMX is emerging.

Enteroinvasive *E coli*

Enteroinvasive *E coli* (EIEC) is a rare cause of diarrhea associated with fever and abdominal pain. The diarrhea is usually watery, but it can be accompanied by fever and leukocytes (ie, dysentery). EIEC is similar to *Shigella* in its ability to invade the colonic mucosa and produce a Shiga-like toxin. Drug resistance is common with TMP-SMX but not with quinolones.

Enteroaggregative *E coli*

Enteroaggregative *E coli* (EAEC) is primarily a problem in infants in developing countries and in HIV-infected adults, although it also can cause traveler's diarrhea. EAEC causes persistent diarrhea that can be watery or bloody. Testing for EAEC requires a tissue culture adherence assay. Quinolones are effective therapy, suggesting that empirical treatment with these agents may be reasonable for patients with HIV who have diarrhea and negative findings on evaluation.

Vibrio

Vibrio species are halophilic and associated with the consumption of raw or undercooked saltwater fish or shellfish (oysters, crabs, and mussels) or contamination of food with seawater.

Vibrio parahaemolyticus is a common cause of diarrhea in the coastal United States and Japan, particularly during warm months.

Several toxins can be produced, resulting in various clinical presentations. The incubation period is less than 1 to 2 days, and the primary symptom is watery diarrhea. Abdominal pain, vomiting, and headaches are also common. Uncommonly, *V parahaemolyticus* may cause frank dysentery and mucosal ulceration. Illness typically lasts 2 to 5 days, and antibiotics usually are not necessary. The role of antibiotics is uncertain, even for patients with severe or prolonged symptoms. If antibiotics are administered, a reasonable choice is ciprofloxacin or doxycycline.

Vibrio cholerae infection is not common in the United States, although sporadic cases occur along the Gulf Coast and in travelers returning from endemic areas (Latin America, Africa, and Asia). The infectious dose is large, although hypochlorhydria decreases it. Cholera toxin can cause profound dehydration from profuse diarrhea (>1 L/h in some cases) and vomiting. However, milder cases (and asymptomatic carriage) are possible. In severe cases, stools are described as "rice water" because of the watery consistency with flecks of mucus. Hypotension, renal failure, and hypokalemic acidosis occur in severe cases and, without aggressive rehydration, often lead to death. Oral rehydration solution can be lifesaving, but severe cases usually require intravenous fluids, with attention to potassium and bicarbonate replacement. Infection can be treated with various antibiotics, most commonly including tetracycline or doxycycline. Azithromycin, erythromycin, or even a single dose of quinolone therapy can be effective, although resistance patterns are emerging.

Vibrio vulnificus also can cause diarrhea, and hemorrhagic bullae may appear. The organism can be acquired through wound contamination from contaminated seawater or by direct consumption, particularly in the summer months. In immunocompromised patients or those with chronic liver disease, systemic infection with sepsis is a risk, with a high mortality rate. These patients should be instructed not to eat or handle raw seafood, particularly oysters.

Yersinia

Yersinia enterocolitica is less common in the United States than in northern Europe. *Yersinia* typically is acquired in cold months from contaminated food, milk, or water and has an incubation period of 4 to 7 days. Many animals can harbor the organism and be a source of infection, which occurs primarily in the terminal ileum. Symptoms range from mild (fever, diarrhea, nausea, and cramps) to severe (reflecting invasion). Uncommonly, *Yersinia* causes bacteremia with sepsis or distant infection. Arthralgias and rash are more common in adults than in children. Postinfectious arthritis also can occur (HLA-B27).

In healthy patients, symptoms typically last 1 to 3 weeks. Antibiotic therapy has not been shown to be of benefit in uncomplicated disease. Patients at risk for sepsis (those with cirrhosis, iron overload, or an immunocompromised state) and those with severe or prolonged symptoms, bacteremia, or distant infections may benefit from antibiotic therapy (tetracycline, quinolones, or TMP-SMX with or without aminoglycosides). *Yersinia ileocolitis* infection can simulate Crohn disease (including extraintestinal manifestations: aphthous ulcers, arthralgias, and erythema nodosum), and right lower quadrant tenderness with mesenteric lymphadenitis can simulate appendicitis.

Parasites

Stool evaluation for ova and parasites is particularly helpful in immunocompromised patients and those with an appropriate exposure or travel history. Most parasites are shed intermittently, and a single stool evaluation is relatively insensitive. To increase sensitivity, 3 or more separate stools should be analyzed.

Giardia lamblia

Giardia lamblia (also known as *Giardia intestinalis* or *Giardia duodenalis*), the most common parasitic infection in the United States, is acquired by the ingestion of water or food contaminated with cysts or by person-to-person spread (eg, day care centers and nursing homes). Cysts can survive for months in the environment and are resistant to chlorination. In the United States, the peak incidence occurs in the summer and early autumn. Excystation occurs in the small bowel, where the trophozoites attach to and damage the mucosa. High-risk groups are travelers to endemic areas, children in day care, patients with immunoglobulin deficiencies, and homosexual men. Symptoms, including watery diarrhea, cramps, nausea, bloating, and flatulence, occur 1 to 2 weeks after ingestion. Patients initially may have acute disease, although diarrhea may be intermittent, leading to a delay in seeking medical attention. Chronic symptoms also may occur and can be associated with malabsorption. Some persons become asymptomatic carriers with long-term cyst passage.

Examination of multiple stools for trophozoites or cysts is reasonably sensitive in cases of acute watery diarrhea. With chronic symptoms or less watery stools, this examination is insensitive and duodenal aspirate and biopsy (organisms or lack of plasma cells) or fecal analysis for *Giardia* antigen may be better. Therapy with metronidazole (250 mg 3 times daily for 5-7 days) or tinidazole (single 2-g dose) is effective. Other treatments include albendazole, furazolidone, or nitazoxanide. Treatment of asymptomatic carriers provides no benefit for the individual but may help prevent outbreaks, for example, among day care or health care workers.

Cryptosporidium

Although *Cryptosporidium* increasingly has been recognized as a pathogen during the AIDS epidemic, it also can cause diarrhea in immunocompetent hosts. Infection commonly is acquired from contaminated water or person-to-person spread. It can resist chlorination, resulting in outbreaks even in industrialized areas. Several US outbreaks have been attributed to contaminated water sources. *Cryptosporidium* invades the small-bowel mucosa and causes inflammation, villous blunting, and malabsorption. In most healthy patients, disease is mild and self-limited, with watery diarrhea, nausea, cramps, and flatulence developing 7 to 10 days after ingestion. Stools may be intermittent and mucoid but should not contain much blood or pus. Diarrhea can last 6 weeks or longer. Headaches, fevers, or myalgias are common. The diagnosis can be made by stool analysis (immunoassays are more sensitive than microscopy) or small-bowel biopsy. In healthy patients, treatment usually is not necessary. Cryptosporidiosis in patients with AIDS is discussed in Chapter 10, "Gastrointestinal Manifestations of Human Immunodeficiency Virus Infection."

Entamoeba histolytica

Amebiasis is the most common parasitic diarrhea in the world, although it is less common in the United States. Most cases in the United States occur in travelers or immigrants from endemic areas (Latin America, Africa, and India) and in homosexual men. Infection is acquired through the ingestion of contaminated food

or water. Amebic cysts undergo excystation in the small bowel and infect the colon. Symptoms begin 7 to 21 days after ingestion and include bloody diarrhea, abdominal pain, fever, and tenesmus, consistent with invasive colitis. Amebic colitis can vary from mild to fulminant, with severe bleeding or perforation. Because the risk of perforation is increased by corticosteroid use, it is important to differentiate amebic colitis from ulcerative colitis. Amebic ulcers are caused by mucosal invasion by trophozoites. The ulcers vary from mild to severe, with the classic description being that of undermined edges leading to a flask-shaped ulcer. Amebae can penetrate the bowel wall, enter the portal circulation, and cause liver or splenic abscesses. Patients with liver abscesses tend to be male, and they may not have a discernible history of colitis. Distant infection (peritonitis, empyema, or central nervous system infection) also can occur. A localized infection surrounded by granulation tissue or a dense fibrous coat (ameboma) can resemble colon cancer.

Diagnosis is made by stool examination. Three or more samples may be needed to make the diagnosis with microscopy, although stool antigen testing and the polymerase chain reaction (PCR) assay for *Entamoeba histolytica* DNA are more sensitive. Metronidazole (750 mg 3 times daily for 7-10 days) is the drug of choice for treating colitis or liver abscesses. Cysts are relatively resistant to metronidazole and require a second agent such as diloxanide furoate, paromomycin, or iodoquinol. Drainage of liver abscesses is not recommended unless rupture is imminent or medical therapy is ineffective.

The human colon can be inhabited by numerous nonpathologic amebae, including *Entamoeba coli, Entamoeba hartmanni*, and *Endolimax nana*. Distinguishing between these organisms and *Entamoeba histolytica* can be difficult with routine microscopy, even for experienced examiners, although serologic testing and stool PCR assay should help.

Blastocystis hominis

Blastocystis hominis is found occasionally on routine stool examinations for ova and parasites. Its pathogenicity is uncertain, particularly in immunocompetent hosts. However, if no other cause for a patient's symptoms is found, a trial of metronidazole can be considered.

Traveler's Diarrhea

Infectious diarrhea affects 40% to 60% of travelers to high-risk areas of Southeast Asia, the Middle East, India, Africa, and Latin America. The incidence of diarrhea varies depending on the specific area visited (eg, urban or rural), the traveler's age, time of year, and local conditions, such as flooding or a cholera outbreak. Bacteria cause 80% to 90% of cases of traveler's diarrhea, and the other 10% to 20% are due to parasites, viruses, or toxins. ETEC is a common cause. The unusual case of prolonged traveler's diarrhea is more likely to be caused by a parasite such as *Giardia intestinalis* or *Cyclospora cayetanensis*. The risk of infection can be decreased by avoiding uncooked foods, local water (including ice), and unpasteurized drinks.

Box 17.3. Antimicrobial Options for Traveler's Diarrhea

Treatment

Ciprofloxacin (500 mg twice daily for 3 d)
Azithromycin (single 1,000-mg dose)
Rifaximin (200 mg 3 times daily for 3 d)

Prophylaxis

Ciprofloxacin (500 mg daily)
Norfloxacin (400 mg daily)
Rifaximin (200 mg 1-2 times daily)
Bismuth subsalicylate (2 tablets 4 times daily)

Symptoms typically begin several days after the person arrives in the area and last for 3 to 5 days. Watery diarrhea, bloating, fatigue, and cramps are common. Bloody diarrhea and high fever are uncommon; their presence suggests an invasive organism and should prompt an evaluation for a specific organism. For most travelers, antibiotic prophylaxis is not recommended. However, patients who are immunocompromised, have severe chronic illness or hypochlorhydria, or are receiving proton pump inhibitor therapy may benefit from prophylaxis (eg, ciprofloxacin, 500 mg daily). Bismuth subsalicylate (2 tablets 4 times daily) is alternative prophylaxis.

Mild cases of traveler's diarrhea can be treated with rehydration and antidiarrheals or bismuth (if no fever, severe pain, or bloody diarrhea) for 1 to 3 days (Box 17.3). For moderate to severe diarrhea, a quinolone is recommended, often together with an antidiarrheal. Ampicillin and TMP-SMX are not recommended because of the high rates of resistance in some areas.

Food Poisoning

From 1988 to 1992 in the United States, 2,423 foodborne outbreaks affected more than 77,000 people. Because of underreporting, the true burden of disease may be 10 to 100 times higher. Most cases of bacterial diarrhea, as indicated in Table 17.3, are acquired from food and can be considered forms of "food poisoning." Also, some bacteria cause acute gastrointestinal tract symptoms from preformed toxins that are ingested with contaminated foods. Common symptoms of food poisoning and typical offending agents are listed in Table 17.6.

Staphylococcus aureus toxin causes 1 to 2 days of severe vomiting, cramps, and diarrhea that begin 2 to 6 hours after ingestion of contaminated food (eg, cream-filled pastries, meat, or potato or egg salad). Severe infection can cause dehydration.

Table 17.6. Food Poisoning Syndromes

Symptoms	*Incubation Period, h*	*Possible Agents*
Acute nausea, vomiting	6	Preformed toxins of *Staphylococcus aureus, Bacillus cereus*
Watery diarrhea	6-72	*Clostridium perfringens, B cereus*, ETEC, *Vibrio cholerae, Giardia*
Inflammatory ileocolitis ("dysentery")	16-72	*Salmonella, Shigella, Campylobacter*, EIEC, EHEC (O157:H7), *Vibrio parahaemolyticus, Yersinia*

Abbreviations: EHEC, enterohemorrhagic *Escherichia coli*; EIEC, enteroinvasive *Escherichia coli*; ETEC, enterotoxigenic *Escherichia coli*.
Data from Guerrant RL, Bobak DA. Bacterial and protozoal gastroenteritis. N Engl J Med. 1991 Aug 1;325(5):327-40.

Clostridium perfringens toxin produces 1 to 2 days of abdominal pain and watery diarrhea that usually begin 8 to 24 hours after ingestion of foods typically prepared in advance and left to sit unrefrigerated (eg, beef, poultry, or gravy). An uncommon strain of *C perfringens* produces the potentially fatal enteritis necroticans, or pigbel, a condition that occurs primarily in poor tropical regions.

Bacillus cereus toxin causes nausea and vomiting that usually occur within 2 to 6 hours after ingestion of contaminated food (eg, pork, creams or sauces, or fried rice) and last 6 to 10 hours. Diarrhea may occur later, probably from a toxin formed in vivo. In healthy hosts, antibiotic therapy is not necessary for these acute forms of food poisoning due to preformed enterotoxins.

Listeria monocytogenes can be found in many foods (eg, hot dogs, lunch meat, and cheeses), and its growth is not substantially inhibited by refrigeration. It can cause gastroenteritis, often with fever, that is typically mild and self-limited, lasting 1 to 2 days. However, in chronically ill or immunosuppressed patients and in the very young, the elderly, and pregnant women, *Listeria* also can cause severe disease, with bacteremia and disseminated infection associated with a high mortality rate. Therapy, usually with ampicillin and gentamicin, is indicated.

Clostridium difficile–Associated Disease

Background

The first case of pseudomembranous colitis was reported in 1893 as "diphtheritic colitis," and the *Clostridium difficile* organism was described in 1935. It was not until the 1970s that *C difficile* was implicated as a causative factor in pseudomembranous colitis. Although *C difficile*–associated disease was described before antibiotics were introduced, most current cases are associated with antibiotic use. Other conditions that can predispose persons to *C difficile*–associated disease include bowel ischemia, surgery, malnutrition, chemotherapy, and critical illness. The spectrum of disease associated with *C difficile* includes an asymptomatic carrier state, diarrhea without colitis, and various degrees of colitis with or without pseudomembranes. Recent increases in the rates of *C difficile* infections may be associated with increased use of antibiotics in the community.

Epidemiology

Since the late 1980s, there has been an increase in the occurrence rate and a more modest clinical spectrum of *C difficile*–associated disease, trends thought to be due to increased use of antibiotics, more aggressive testing, and early intervention. Recent data reflect the health care burden of *C difficile* infection: an additional hospital cost of more than $3,000 per patient and an extra length of stay of 3.6 days, leading to an estimated cost in the United States in excess of $1 billion per year.

Clostridium difficile is more common in hospitalized adults and in patients receiving antibiotic therapy. Recently, however, there has been an increase in the number of cases of *C difficile*–associated diarrhea in the absence of prior antibiotic exposure. Up to 50% of infants and children carry the bacterium, but pseudomembranous colitis is rare in this age group. The incidence of antibiotic-associated diarrhea varies from 5% to 39%, depending on the antibiotic used, and most cases are due to the antibiotic and not to infection with *C difficile*, particularly in outpatients. Pseudomembranous colitis occurs in only 10% of cases of antibiotic-associated diarrhea. In contrast to antibiotic-associated diarrhea, most cases of pseudomembranous colitis are due to *C difficile*.

Risk factors for *C difficile*–associated disease may include older age (>70 years), uremia, burns, abdominal surgery, cancer, inflammatory bowel disease, use of gastric acid–suppressive medication, and hospitalization in an intensive care unit. It is not known whether groups of patients with these risk factors are more exposed to nosocomial infections or are more susceptible to *C difficile*–associated disease because of their specific illnesses.

Case Presentation

A 75-year-old man sought care for a 2-day history of crampy lower abdominal pain, nonbloody diarrhea, tenesmus, and fever. He recently completed a course of antibiotic therapy for pneumonia. On physical examination, he appeared ill, with a temperature of 38.3°C, normal blood pressure, and a pulse rate of 98 beats per minute. The abdomen was mildly distended and tender without guarding or rebound. Laboratory studies showed leukocytosis of 13,400/μL, with 15% band forms. Stool analysis showed many leukocytes, and *C difficile* toxin was detected. Abdominal radiography showed mild ileus but no dilatation of the colon. Treatment with metronidazole, 500 mg 3 times daily by mouth, promptly improved the symptoms.

Clinical Presentation

The time between the initiation of antibiotic therapy and the appearance of clinical symptoms varies from 1 day to 6 weeks, most commonly 3 to 9 days. However, symptoms may occur after a single dose of antibiotics (including topical antibiotics), or they may not begin until several weeks after antibiotic therapy has been discontinued.

Presentation may range from only loose stools to toxic megacolon (nausea, vomiting, high-grade fever, and ileus) and colonic perforation. Typically, the disease manifests with watery or mucoid diarrhea, abdominal pain, and low-grade fever. Stools may contain small amounts of blood. Extraintestinal manifestations, such as arthritis, are rare. Diarrhea may cause dehydration and electrolyte depletion. The overall mortality rate is low (2%-3%), although it is higher among elderly or debilitated patients (10%-20%) and patients with fulminant colitis or toxic megacolon (30%-80%). In some patients (5%-19%), disease is localized to the proximal colon; these patients may present with an acute abdomen and localized rebound tenderness, but no diarrhea, and normal findings on sigmoidoscopy.

Despite successful treatment, 10% to 25% of patients have disease relapse, regardless of the therapeutic agent used. Disease relapse usually responds well to re-treatment with metronidazole or vancomycin, but the risk of additional recurrences is high.

Differential Diagnosis

Staphylococcal enterocolitis and typhlitis can occur in patients receiving chemotherapy, and these patients can have a presentation similar to that of patients who have *C difficile*–associated disease. Exacerbation of Crohn disease and ulcerative colitis can simulate *C difficile*–associated disease, and, importantly, *C difficile* infection can cause a symptom flare in patients with inflammatory bowel disease. Other disorders in the differential diagnosis include chemical colitis (chemotherapy or gold), ischemic colitis, and other infections (from *Campylobacter, Salmonella, Shigella, E coli, Entamoeba, Listeria*, and cytomegalovirus).

Pathophysiology

The development of *C difficile*–associated disease requires an alteration in the normal gut flora or mucosal immunity, the acquisition and germination of spores, an overgrowth of *C difficile*, and the production of toxin. Toxin A binds to mucosal receptors and causes cytotoxicity by disrupting cytoplasmic microfilaments and inducing apoptosis. Toxin B can then enter the damaged mucosa and cause further cytotoxicity, resulting in hemorrhage, inflammation, and cellular necrosis. The toxins also interfere with protein synthesis, stimulate granulocyte chemotaxis, increase capillary permeability, and promote peristalsis. In severe cases, inflammation and necrosis may involve deeper layers of the colon and result in toxic dilatation or perforation.

A new hypervirulent strain of *C difficile* (NAP1/BI/027) has been linked with selected outbreaks of severe disease in recent years. An epidemic strain of NAP1/BI/027 is known to produce a binary toxin not produced by other *C difficile* strains. The epidemic strain also produces larger quantities of toxins A and B in vitro and is resistant to fluoroquinolones in vitro.

Diagnostic Testing

Diagnosis is based on a combination of clinical findings, laboratory test results, and occasionally endoscopy. Leukocytosis and hypoalbuminemia are not uncommon. Fecal leukocytes can be seen, but their absence does not exclude colitis. Stool culture for *C difficile* is relatively demanding and has low predictive value.

Cytotoxicity assays are considered positive when cultured cells show cytopathic changes on exposure to stool filtrates. The result is then confirmed by neutralizing these effects with specific antitoxins. This is considered the standard diagnostic method because of its high sensitivity and specificity. However, cytotoxicity assays are expensive and time consuming.

Enzyme-linked immunosorbent assay (ELISA) for the detection of toxin A or B is less expensive and faster than tissue culture and, thus, is preferred at many centers. Sensitivity is lower (75%-85%) than for cytotoxic assays, but performing the test on 2 or 3 separate stools should increase sensitivity to 90% to 95%. In addition, proper storage and handling may prevent toxin degradation and improve sensitivity. A newer ELISA to detect the presence of either toxin (TOX A/B test; Techlab, Inc) has excellent specificity and improved sensitivity compared with testing for either toxin alone, because some strains of *C difficile* may produce only 1 toxin or the other. In July 2009, a PCR assay based on the stool toxin assay was introduced, with a sensitivity of approximately 95% with use of a single stool sample. This PCR-based assay has now become the diagnostic test of choice in many centers because of its greater sensitivity.

Although endoscopic findings may be normal in patients with mild *C difficile*–associated disease, most patients have abnormal mucosa. Flexible sigmoidoscopy is diagnostic in most patients, but colonoscopy may be required in about 10% of patients when disease is localized above the splenic flexure. Endoscopy may be the fastest means of suggesting the diagnosis, but in patients with severe disease, it is hazardous and should be avoided. Colitis may range from minimal erythema or edema to ulceration, often with nodular exudates that may coalesce to form yellow "pseudomembranes" consisting of mucus and fibrin filled with dead leukocytes and mucosal cells (Figure17.1).

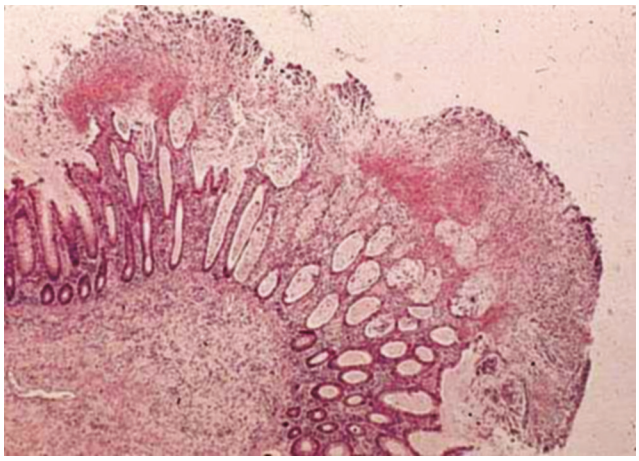

Figure 17.1. Pseudomembranous Colitis. Typical histologic appearance is shown (hematoxylin-eosin).

Treatment of Primary Infection

For mild disease, supportive therapy alone (without antibiotic treatment) may be sufficient, including rehydration and discontinuation of treatment with the offending antibiotic. Antidiarrheal agents and narcotics should be avoided because they may prolong exposure to toxins and result in more severe colitis. Specific antibiotic therapy should be prescribed if supportive therapy fails, if treatment with the offending antibiotic cannot be discontinued, or if symptoms are severe. For severe disease, hospitalization for antibiotic therapy and intravenous hydration may be necessary. When *C difficile*–associated disease is suspected in elderly and severely ill patients, empirical antibiotic therapy should be started before test results are known.

Metronidazole is inexpensive and effective and has response and relapse rates comparable to those of vancomycin. The usual oral dose is 500 mg 3 times daily for 14 days. Because of concerns about cost and resistance with vancomycin, metronidazole is the preferred first-line therapy for patients with mild disease (white blood cell count <15,000/μL and normal serum creatinine). For patients presenting with more severe disease (white blood cell count >15,000/μL and elevated serum creatinine), vancomycin is recommended at a dose of 125 mg 4 times daily for 14 days. Metronidazole has more adverse effects and is not recommended for children or pregnant women. If the patient's condition does not improve promptly (2-3 days), the situation should be reassessed and, if the diagnosis is secure, vancomycin should be substituted for metronidazole.

Vancomycin is a reliable but more expensive treatment, with response rates of 90% to 100%, and is the preferred agent for severely ill patients. Because oral vancomycin is poorly absorbed, a high stool concentration can be achieved without systemic adverse effects. A higher dose (250-500 mg 4 times daily) can be given to severely ill patients.

Parenteral therapy is less effective than oral therapy, but when necessary (eg, paralytic ileus), intravenous metronidazole (500-750 mg 3 or 4 times daily) is recommended, perhaps supplemented by vancomycin (500 mg 4 times daily) through a nasogastric tube or by enema.

Anion exchange resins work by binding toxin. Cholestyramine (4 g 4 times daily) can help decrease symptoms in mild disease, but when it has been given alone, results have been disappointing, with variable but generally low cure rates. Obstipation is the most

common adverse effect. Because cholestyramine binds vancomycin, they should not be given simultaneously.

Treatment of Recurrent Infection

Recurrent disease usually responds well to re-treatment with metronidazole or vancomycin at standard doses. For multiple or refractory recurrences, several therapeutic options are available. One is a prolonged course of vancomycin therapy, followed by gradual tapering (eg, 125 mg 4 times daily for 4-6 weeks, 125 mg twice daily for 1 week, 125 mg daily for 1 week, and 125 mg every other day for 1 week, followed by 125 mg every 72 hours for 2 weeks). An alternative to prolonged antibiotic tapering is vancomycin 500 mg 4 times daily for 10 to 14 days, followed by rifaximin 400 mg twice daily for 14 days. Another option is fidaxomicin 200 mg twice daily for 10 days. This has been shown to be as effective as vancomycin for clearing *C difficile* initially and is associated with a lower likelihood of recurrent disease (recurrence rate: 25% with vancomycin, 15% with fidaxomicin). The use of fidaxomicin is restricted because it is expensive.

Fecal microbiota transplantation is showing tremendous promise in difficult-to-treat cases of recurrent *C difficile* infection. The fecal material is administered into the proximal colon at colonoscopy. This therapy has led to cure rates of approximately 90% in cases of medically refractory disease and is an area of considerable research and growth.

Surgical Treatment

Surgical treatment usually is not necessary for *C difficile*–associated disease. Diverting ileostomy or colectomy is performed for severe refractory disease or for complications such as perforation or megacolon. Because the risk of complications increases markedly after several days of ineffective therapy, some advocate surgery for severe disease that does not respond after 2 to 7 days of treatment.

Prevention

The spores of *C difficile* can survive for up to 5 months in the environment, and a primary mode of infection is the hands of hospital personnel or contaminated objects. Therefore, prevention has a crucial role in disease management and can be facilitated by the prudent use of antibiotics, routine hand washing, disinfection of potentially contaminated objects, and isolation of infected patients, with the use of gloves for patient contact.

Treatment of asymptomatic carriers is not recommended because it may prolong the carrier state, which usually resolves spontaneously. Restricting the use of broad-spectrum antibiotics has decreased the rate of *C difficile*–associated disease at some institutions.

Summary

Clostridium difficile is a spore-forming toxigenic bacterium that causes diarrhea and colitis, typically after antibiotic therapy. The clinical presentation ranges from self-limited diarrhea to fulminant colitis and toxic megacolon. Although in most cases the disease is mild and responds quickly to treatment, *C difficile* colitis may be severe, especially if diagnosis and treatment are delayed. Recurrence can be a serious problem. Prevention is achieved best by limiting the use of broad-spectrum antibiotics and by following good hygienic techniques and universal precautions to limit the transmission of the bacteria. A high degree of awareness results in early diagnosis and treatment and potentially decreases the incidence of complications.

Diverticular Disease

In Western societies, colonic diverticulosis affects 5% to 10% of the population older than 45 years and 80% of those older than 85 years. Patients with uninflamed and nonbleeding diverticula are asymptomatic. Approximately 20% of patients with diverticula have an episode of symptomatic diverticulitis. Diverticular hemorrhage is the second most common cause of colonic bleeding after vascular lesions.

Pathophysiology

Diverticulosis affects predominantly the sigmoid colon but may involve the entire colon. High luminal pressure is believed to cause mucosal protrusion through weak areas where the vasa rectae penetrate the bowel wall, resulting in diverticula. There is an association between diverticulosis and a Western diet high in refined carbohydrates and low in dietary fiber; whether this is a causal association is unproved. If the neck of a diverticulum is obstructed, it may distend and lead to bacterial overgrowth and invasion, often with perforation, which is generally walled off by the adjacent mesocolon or appendices epiploicae.

Classification

Stage I diverticulitis is characterized by small confined pericolonic abscesses, and stage II disease includes larger confined pericolonic collections. Stage III involves generalized suppurative peritonitis (perforated diverticulitis); because the diverticular neck is generally obstructed by a fecalith, peritoneal contamination by feces may not occur. Stage IV indicates fecal peritonitis.

Clinical Features

Symptoms of diverticulitis include lower abdominal pain, fever, and altered bowel habits (typically, diarrhea). The stool may contain trace amounts of blood, but profuse bleeding is very uncommon. Dysuria, urinary frequency, and urinary urgency reflect bladder irritation, whereas pneumaturia, fecaluria, and recurrent polymicrobial urinary tract infection suggest a colovesical fistula. Physical findings include fever, left lower quadrant tenderness, or a mass.

Complications

Rupture of a peridiverticular abscess or uninflamed diverticulum causes peritonitis, occurs more commonly in elderly and immunosuppressed persons, and is associated with a high mortality rate. Repeated episodes of acute diverticulitis may lead to colonic obstruction. Jaundice or hepatic abscesses suggest pylephlebitis. A massively dilated (>10 cm) cecum, signs of cecal necrosis (ie, air in the bowel wall), or marked tenderness mandates immediate surgical consultation. Colovesical and, less frequently, colovaginal and colocutaneous fistulas may occur.

Diagnostic Studies

A contrast enema shows diverticula but not diverticular inflammation. Moreover, contrast studies may cause perforation. If the

Box 17.4. Treatment of Diverticulitis

Patient has a mild first attack and tolerates oral intake: Provide outpatient therapy with a liquid diet and oral broad-spectrum antibiotics (eg, ciprofloxacin and metronidazole). After the acute attack has resolved, a high-fiber diet and colonoscopy (to exclude cancer) are advisable. Approximately 5%-10% of patients will have a second attack within 2 years.

Patient has severe pain, cannot tolerate oral intake, and has persistent symptoms despite adequate outpatient therapy: Hospitalize, give nothing by mouth, and administer broad-spectrum intravenous antibiotics. Perform computed tomography to exclude abscess or perforation. Consider computed tomographically guided percutaneous drainage of an abscess to control systemic sepsis, permitting a single-stage surgical procedure, if necessary, at a later stage.

Patient requires surgery: Emergency operation is indicated for peritonitis, uncontrolled sepsis, perforation, and clinical deterioration. Indications for elective surgery include fistula formation, stricture, and recurrent diverticulitis.

clinical features are highly suggestive of diverticulitis, imaging studies are unnecessary. If the diagnosis is uncertain or if an abscess is suspected, computed tomography is preferred, although the results may be false-negative in up to 20% of cases. Ultrasonography also may show diverticular inflammation, but it is more operator-dependent than computed tomography, and abdominal tenderness may preclude application of sufficient external pressure. Flexible sigmoidoscopy is necessary only if carcinoma or colitis is a concern.

Treatment

Treatment is influenced by severity, ability to tolerate oral intake, previous history of diverticulitis or bleeding, and complications (Box 17.4). If surgical treatment can be deferred until the acute inflammation heals, a single-stage primary resection and reanastomosis, perhaps laparoscopically, can be accomplished with minimal morbidity and mortality. For emergency indications, the first stage of a 2-stage procedure involves resection of the diseased segment and creation of an end colostomy with oversewing of the distal colonic or rectal stump (Hartmann procedure). Colonic continuity may be reestablished in a second operation.

Suggested Reading

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18

Colorectal Neoplasms[a]

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Colorectal cancer is primarily a disease of urban, industrialized societies. In the United States, the lifetime risk of colorectal cancer is approximately 6%. Recent data have suggested that the incidence rates of colorectal cancer may be decreasing gradually in some subgroups of the population. However, the mechanisms underlying these favorable trends have not been defined completely. Several national organizations have endorsed screening and surveillance guidelines, which undoubtedly have contributed to more effective prevention of colorectal cancer.

Clinical Features

Definition

Most cases (>95%) of colorectal cancer are adenocarcinomas. Less common cancer subtypes include lymphoma, carcinoid, and leiomyosarcoma. Metastatic lesions to the colorectum can include lymphoma, leiomyosarcoma, malignant melanoma, and adenocarcinomas of the breast, ovary, prostate, lung, and stomach. Because of the relative rarity of these other malignancies, the term *colorectal cancer* is used throughout the rest of this chapter to refer to *primary adenocarcinoma*. The term *colorectal neoplasia* is used to refer to either *malignant adenocarcinomas* or *premalignant adenomas*, as described in more detail below.

Presentation

Clinical manifestations of colorectal cancer often are related to tumor size and location. Common signs and symptoms with proximal neoplasms (cecum to splenic flexure) include ill-defined abdominal pain, weight loss, and occult bleeding. Patients with distal neoplasms (descending colon to rectum) may present with altered bowel habits, decreased stool caliber, or hematochezia (or a combination of these). Colonoscopy is the test of choice for the diagnostic evaluation of any signs or symptoms suggestive of colorectal cancer because tissue specimens can be obtained at the time of visual inspection. Up to 7% of patients with colorectal cancer may have additional, synchronous malignancies in the colon or rectum at the time of the index cancer diagnosis. At the initial diagnosis of colorectal cancer, 39% of patients have localized disease, 36% have regional metastases, and 19% have distant metastases. Distant metastases typically occur in the liver, peritoneal cavity, and lungs. Less common sites of metastases are the adrenal glands, ovaries, and bones. Central nervous system metastases are rare.

Adenoma-Carcinoma Sequence

Most colorectal cancers are thought to develop through an ordered series of events: normal colonic mucosa develops into mucosa at risk, which develops into adenoma, which develops into adenocarcinoma. Indirect evidence to support this adenoma-carcinoma

[a] Portions previously published in Limburg PJ, Ahlquist DA. Colorectal adenocarcinoma. In: Johnson LR, editor. Encyclopedia of gastroenterology. Amsterdam: Elsevier Academic Press; c2004. p. 457-66 and Hawk E, Lubet R, Limburg P. Chemoprevention in hereditary colorectal cancer syndromes. Cancer. 1999 Dec 1;86(11 Suppl):2551-63. Used with permission.

Abbreviations: AFAP, attenuated familial adenomatous polyposis; COX-2, cyclooxygenase 2; CT, computed tomography; EGFR, epidermal growth factor receptor; FAP, familial adenomatous polyposis; FOLFIRI, 5-fluorouricil, leucovorin, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; MAP, MutYH-associated polyposis MSI, microsatellite instability; SEER, Surveillance, Epidemiology, and End Results; VEGF, vascular endothelial growth factor

sequence includes the following: 1) prevalence rates cosegregate within populations, 2) subsite distribution patterns within the colorectum are similar, 3) benign adenomatous tissue is often juxtaposed with invasive cancer in early-stage malignancies, and 4) incidence rates of colorectal cancer are decreased by endoscopic polypectomy. Also, specific molecular alterations have been associated with the adenoma-carcinoma sequence (Figure 18.1). The *APC* tumor suppressor gene is considered the "gatekeeper" and is mutated in approximately 85% of all colorectal cancers. *KRAS* is the most frequently activated oncogene in colorectal neoplasms and is mutated in approximately 50% of large (≥1 cm) adenomas and adenocarcinomas. Expression of the *p53* gene is altered later in carcinogenesis; chromosomal loss of both *p53* and *p53* mutations is more common in malignant neoplasms (70%-80%) than in benign neoplasms. DNA sequence variation in normally stable regions, termed microsatellite instability (MSI), is found in 12% to 17% of colorectal tumors, particularly those in the right colon. MSI is often found in association with methylation of gene promotors, including a DNA mismatch repair gene (*MLH1*), and with mutation of the *BRAF* oncogene.

Polyp Subtypes

Adenomatous polyps are considered to have malignant potential, whereas hyperplastic, inflammatory, and hamartomatous (juvenile) polyps generally do not. Sessile serrated adenomas confer an increased risk of future colorectal cancer and have been implicated in being precursor lesions for microsatellite unstable colorectal cancer. Adenomas can be classified further as tubular (70%-85%), villous (<5%), or tubulovillous (10%-25%) on the basis of their glandular histologic features and as low-grade or high-grade on the basis of their degree of dysplasia. "Advanced" adenomas are associated with an increased risk of colorectal cancer and usually are defined by 1) large size (≥1 cm), 2) any villous histologic features, or 3) high-grade dysplasia. Multiple (≥3) synchronous adenomas also are associated with an increased risk of colorectal cancer.

Staging and Prognosis

The American Joint Commission on Cancer system is commonly used to stage colon and rectal cancers (Table 18.1). It subcategorizes the pathologic stage of the tumor to correlate with prognosis. This classification system subdivides pathologic stages further to account for worse prognosis on the basis of the depth of tumor invasion, number of metastatic regional nodes, and number of metastatic sites. For colon cancers, the preoperative, or clinical, stage typically is determined by physical examination, computed tomography (CT), and chest radiography. For rectal cancer, endoscopic ultrasonography or pelvic magnetic resonance imaging can provide additional information about the depth of tumor invasion and regional lymph node status. Before neoadjuvant radiochemotherapy, rectal cancers may be given a clinical stage designated by a lowercase letter *c* after the T or N category; after neoadjuvant treatment, rectal cancers are given a pathologic stage designated by the lowercase letters *yp* preceding the TNM categories. The final colorectal cancer stage incorporates pathology review of the resected tumor tissue. Pathologic stage

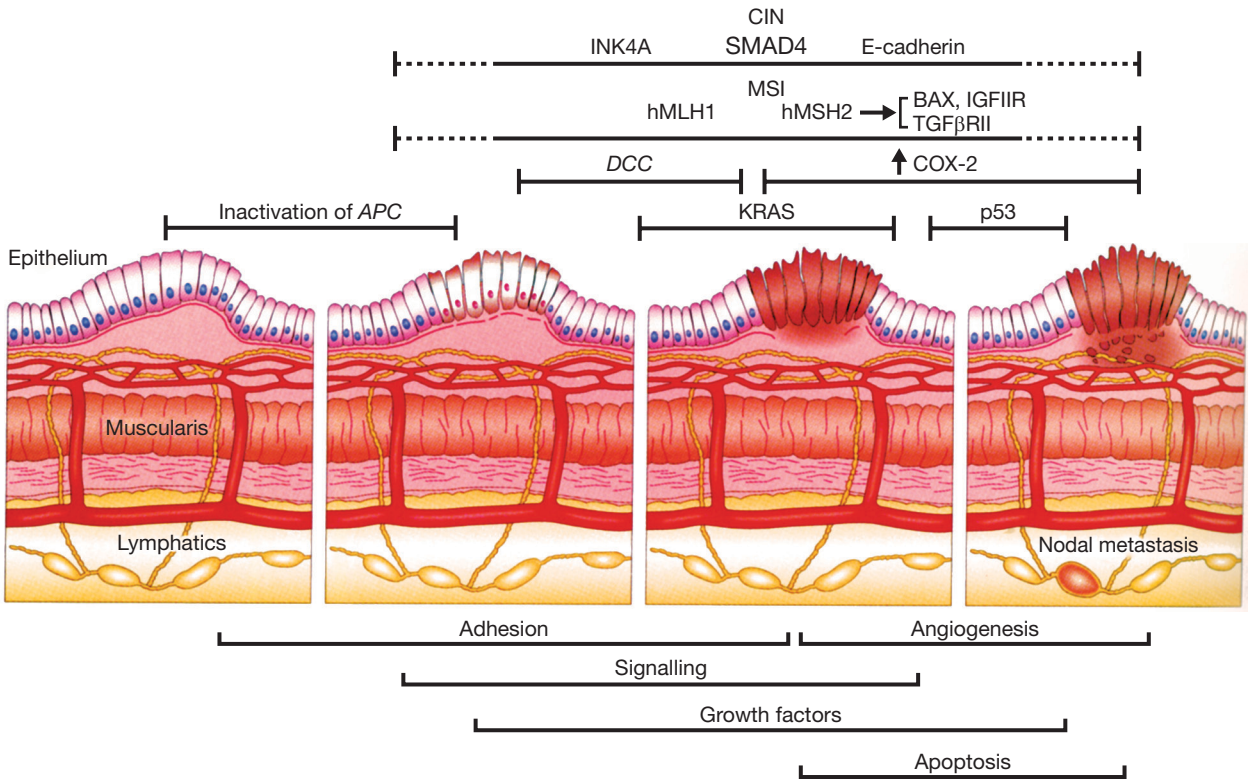

Figure 18.1. Adenoma-Carcinoma Sequence and the Associated Molecular Alterations Involved in Colon Cancer Development. *APC* indicates adenomatous polyposis coli tumor suppressor gene; CIN, chromosomal instability; COX-2, cyclooxygenase 2; *DCC*, deleted in colorectal cancer gene; MSI, microsatellite instability. (Adapted from Van Schaeybroeck S, Lawler M, Johnston B, Salto-Tellez M, Lee J, Loughlin P, et al. Colorectal cancer. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, editors. Abeloff's clinical oncology. 5th ed. Philadelphia [PA]: Elsevier Churchill Livingstone; c2014. p. 1278-335.e14. Used with permission.)

Table 18.1. Colorectal Cancer Staging

Stage	*TNM Classification*[a,b]
0	Tis N0 M0
I	T1 or T2 N0 M0
IIA	T3 N0 M0
IIB	T4a N0 M0
IIC	T4b N0 M0
IIIA	T1-T2 N1/N1c M0
	T1 N2a M0
IIIB	T3-T4a N1/N1c M0
	T2-T3 N2a M0
	T1-T2 N2b M0
IIIC	T4a N2a M0
	T3-T4a N2b M0
	T4b N1-N2 M0
IVA	Any T any N M1a
IVB	Any T any N M1b

[a] T category (primary tumor): Tis, tumor confined to mucosa; T1, tumor invades the submucosa; T2, tumor invades through the submucosa and into the muscularis propria; T3, tumor invades through the muscularis propria and into pericolorectal tissues; T4, tumor invades through the entire colorectal wall and into nearby tissues and organs.
[b] Prognosis varies with the following: 1) Depth of tumor penetration: T4a penetrates the surface of the visceral peritoneum and T4b invades into or adheres to other organs. 2) Number of nodes: N0 (no nodal metastases); N1a (metastasis in 1 regional node); N1b (metastasis in 2-3 nodes); N2a (metastasis in 4-6 nodes); and N2 (metastasis in ≥7 nodes). 3) Metastatic sites: M0 (no distant metastasis); M1a (single metastatic site); and M1b (multiple metastatic sites).
Adapted from Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A 3rd; American Joint Committee on Cancer, editors. AJCC cancer staging handbook: from the AJCC cancer staging manual. 7th ed. New York (NY): Springer; c2010. p. 174. Used with permission.

is the best predictor of survival. The overall 5-year survival rate for colorectal cancer is approximately 64%. Stage-specific 5-year disease-free survival rates for colon cancer are as follows: stage I, 93%; stage IIa, 85%; stage IIb, 72%; stage IIIa, 83%; stage IIIb, 64%; stage IIIc, 44%; and stage IV, 8%. Five-year survival rates for rectal cancer are generally similar.

Epidemiologic Factors

General Distribution

Worldwide, colorectal cancer ranks fourth in cancer incidence for men and third for women. However, the incidence rates vary by global region (by a ≥25-fold difference). Areas with the highest reported incidence rates of colorectal cancer include North America, Australia and New Zealand, Western Europe, and Japan. Conversely, most parts of Africa and Asia report low incidence rates. In the United States, age-adjusted incidence and mortality rates of colorectal cancer in women are 41.4 per 100,000 and 14.5 per 100,000, respectively. For men, the respective rates are higher: 55.7 per 100,000 and 20.7 per 100,000. From 1998 to 2008, the annual percentage change in colorectal cancer incidence rates was −2.6% for men and −2.0% for women. However, for persons 20 to 49 years old, incidence rates of colorectal cancer from 1992 to 2005 increased 1.5% per year for men and 1.6% per year for women.

Race and Ethnicity

Of the 5 major racial-ethnic population subgroups monitored by the Surveillance, Epidemiology, and End Results (SEER) program, African Americans have the highest incidence and mortality rates for colorectal cancer. Although this likely is explained, at least partly, by differences in the stage of disease at the time of diagnosis, the survival gap persists when within-stage comparisons are made.

Anatomical Subsite

Anatomical subsites of the colorectum differ in their embryologic origin, physiologic function, and vascular supply. Differences in the morphology, histology, and genetics of colorectal cancer have been observed across regions within the large bowel. Subsite-specific incidence rates also differ, and the proportion of cases of colorectal cancer located in the proximal colon appears to be increasing compared with the proportion of cases in the distal colon and rectum.

Age

As with most malignancies, the incidence rates of colorectal cancer increase with advancing age. Fewer than 5% of cases occur among persons younger than 45 years. SEER data suggest that age-specific incidence rates of colorectal cancer begin to increase more rapidly during the fifth decade. The prevalence of adenomatous polyps also increases with age, with estimates of 30% at 50 years, 40% to 50% at 60 years, and 50% to 65% at 70 years. Also, several important clinical features of adenomas may be age-related. In the National Polyp Study, the risk of having a polyp with high-grade dysplasia was 80% higher among participants 60 years or older than among younger participants.

Personal History of Colorectal Neoplasia

Persons with a personal history of colorectal adenomas or adenocarcinomas are at increased risk (up to 6-fold) for additional, or metachronous, neoplasms. Adenoma characteristics associated with future tumor development include large size (≥1 cm), villous histology, and 3 or more lifetime colonic adenomas. Neither rectosigmoid hyperplastic polyps nor small, solitary tubular adenomas are strong risk factors for metachronous neoplasms. After resection of colorectal cancer, the annual incidence rate of a second primary colon or rectal cancer has been estimated at 0.35%.

Family History of Colorectal Neoplasia

Familial clustering is observed in approximately 15% of all cases of colorectal cancer, including patients with heritable cancer syndromes (see below). In the absence of an identifiable syndrome, a strong family history of colorectal neoplasia (typically defined as having 1 first-degree relative with colorectal neoplasia diagnosed before age 60 years or ≥2 first-degree relatives with colorectal neoplasia diagnosed at any age) appears to confer an approximately 1.5- to 2-fold increase in the risk of colorectal cancer.

Inflammatory Bowel Disease

Chronic ulcerative colitis is associated with an increased risk of colorectal cancer. In the United States and Europe, the incidence of colitis-associated cancers appears to have decreased in recent decades but remains strongly correlated to the duration of chronic colitis. The extent of colitis has been positively associated with colorectal cancer risk (ie, the risk with pancolitis is greater than the risk with distal colitis, which is greater than the risk with proctitis), but the effects of disease activity have not been defined completely. Primary sclerosing cholangitis and a family history of colorectal cancer are additional risk factors. However, the

effects of disease activity on the risk of colorectal cancer are not conclusively known. Fewer data are available on the association between Crohn disease and colorectal cancer, but the risk appears to be comparable to that of chronic ulcerative colitis when more than one-third of the colon has been involved after a similar duration. Current data do not support an increased risk of colorectal cancer for patients with lymphocytic or collagenous colitis.

Dietary Components

Excess body weight has been associated with a 1.5- to 2-fold increase in the risk of colorectal cancer, although not all observational studies have demonstrated consistent results. Red meat, particularly when consumed with a heavily browned surface, has been proposed as a risk factor for both benign and malignant colorectal neoplasia.

Vegetables and fruits contain a wide array of potentially anticarcinogenic substances that may function through 1 or several independent or codependent mechanisms. Generally, vegetable consumption has been 1 of the most consistent predictors of reduced risk of colorectal cancer, but fruit consumption appears to be associated less strongly with reductions in large-bowel tumorigenesis.

Fiber enhances stool bulk, decreases the concentration of procarcinogenic secondary bile acids, and increases the concentration of anticarcinogenic short-chain fatty acids. Although multiple case-control studies initially suggested a protective effect from increased dietary fiber, subsequent intervention trials have not shown appreciable reductions in the risk of colorectal cancer.

Calcium binds to intraluminal toxins and also influences mucosal proliferation within the colorectum. In 1 clinical trial, calcium supplementation was associated with a statistically significant 19% decrease in the recurrence of adenoma in postpolypectomy patients after 4 years. However, in another large, randomized, controlled trial of postmenopausal women, calcium and vitamin D supplementation for 7 years had no appreciable effect on incident colorectal cancer.

Antioxidants (including retinoids, carotenoids, ascorbic acid, α-tocopherol, and selenium) have been hypothesized to prevent carcinogen formation by neutralizing free radical compounds. So far, observational and experimental data have been unimpressive, with the exception that selenium decreased the risk of colorectal cancer by 58% when measured as a secondary end point in a skin cancer prevention study.

Folate and methionine supply methyl groups necessary for critical cellular functions such as nucleotide synthesis and gene regulation. Particularly in the context of excess alcohol consumption, dietary deficiencies of these compounds may be a risk factor for colorectal cancer. Nonetheless, in a recent multicenter clinical trial of participants with a previous history of benign colorectal neoplasia, folic acid 1 mg daily was associated with an increased risk of both recurrent advanced adenomas and noncolorectal cancers.

Lifestyle

Alcohol induces cellular proliferation, blocks methyl group donation, and inhibits DNA repair. Many observational studies have suggested a 2- to 3-fold increase in the risk of colorectal cancer with excess alcohol consumption, although a meta-analysis of 27 case-control and cohort studies found only a 10% increase in risk among daily alcohol users.

Tobacco smoke contains numerous putative carcinogens, including polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines. On the basis of data from several large cohort studies, smoking appears to be a risk factor for colorectal cancer after a prolonged latency of 20 or more years.

Physical activity has been associated consistently with a 40% to 50% decrease in the risk of colorectal cancer, particularly in the distal colon, through the stimulation of intestinal transit, decreased prostaglandin E_2 levels, or other undefined mechanisms.

Other

In a meta-analysis of data from 15 observational studies, patients with type 2 diabetes mellitus had a 30% increase in the risk of colorectal cancer compared with those without diabetes. Insulin resistance has been proposed as the underlying mechanism of tumorigenesis.

Persons with acromegaly may be predisposed metabolically or anatomically to higher risks of colorectal cancer. Because of the relative rarity of this condition, most observational studies have lacked adequate statistical power, but the preponderance of evidence supports a positive risk association.

Cholecystectomy results in an altered fecal bile acid composition. Two meta-analyses have reported moderately increased risks of 11% to 34% for colorectal cancer (mainly in the proximal colon) after gallbladder surgery.

Heritable Syndromes

Cases of hereditary colorectal cancer account for approximately 15% of all large-bowel malignancies. Several well-defined syndromes have been recognized, as discussed below. It is important to remember that patients with gene mutations are also at increased risk for target organ cancers outside the colorectum.

Familial Adenomatous Polyposis

Germline mutations in the *APC* gene form the basic molecular foundation for familial adenomatous polyposis (FAP) (an autosomal dominant condition). As many as 1 in 5 cases may result from new-onset spontaneous mutations. The estimated prevalence is 1 per 5,000 to 7,500 persons. Additional but unidentified genetic and environmental factors seem likely to influence the clinical manifestations of FAP because phenotypic features vary widely despite similar inherited *APC* mutations. The hallmark lesion of FAP is diffuse colorectal polyposis, and, typically, hundreds to thousands of adenomas develop during adolescence. Other findings include duodenal adenomas, gastric (fundic) gland hyperplasia, mandibular osteomas, and supernumerary teeth. In the absence of prophylactic colectomy, colorectal carcinoma inevitably is diagnosed in patients with FAP at a mean age of approximately 40 years. Even after colectomy, patients have an increased risk of cancer, particularly in the periampullary region of the duodenum and in the retained rectal remnant (if partial colectomy was performed).

Gardner syndrome is a variant of FAP in which patients with *APC* mutations have the same phenotypic features as in classic FAP, but they also can have osteomas of the skull and long bones, congenital hypertrophy of the retinal pigmented epithelium, desmoid tumors, epidermoid cysts, fibromas, and lipomas.

Attenuated Familial Adenomatous Polyposis

Compared with classic FAP, attenuated FAP (AFAP) is associated with relatively fewer adenomas (<100) and a later onset of

colorectal cancer (approximate age at onset, 55 years). About 40% of these cases are associated with germline *APC* mutations. Because both the adenomas and the cancers appear to arise in the proximal colon, at-risk family members should have screening with full colonoscopy rather than with flexible sigmoidoscopy, as recommended for screening in classic FAP kindreds.

Lynch Syndrome

Lynch syndrome (also called hereditary nonpolyposis colorectal cancer) is an autosomal dominant syndrome characterized by early-onset colorectal cancer, usually located in the proximal colon, and increased risk of extracolonic malignancies (in the uterus, ovaries, stomach, urinary tract, small bowel, and bile duct). The clinical criteria for considering a person to be at risk for Lynch syndrome are the Amsterdam criteria (Box 18.1). The syndrome has been associated recently with mutations in at least 5 DNA mismatch repair genes (*MLH1, MSH2, PMS1, PMS2*, and *MSH6*), which maintain nucleic acid sequence integrity during replication. Adenomas are believed to precede carcinomas in most instances, and colorectal cancer develops in 75% to 80% of patients with Lynch syndrome, at a median age of 46 years. It has been reported that for persons with Lynch syndrome, regularly performed colonoscopy with polypectomy can decrease the risk of large-bowel adenocarcinoma by approximately 60%.

Turcot Syndrome

Turcot syndrome is a familial predisposition for both colonic polyposis and central nervous system tumors. It likely is a constellation of molecular features that can be variants of either FAP or Lynch syndrome. Patients with early-onset colonic polyposis associated with *APC* mutations tend to have medulloblastomas (an FAP variant), whereas those with DNA mismatch repair gene mutations are prone to the development of glioblastoma multiforme (a Lynch syndrome variant). Of interest, glioblastoma multiforme that arises in Turcot syndrome tends to occur at an earlier age and carry a better prognosis than the sporadic form of the tumor.

Muir-Torre Syndrome

Patients with Muir-Torre syndrome have sebaceous neoplasms, urogenital malignancies, and gastrointestinal tract adenocarcinomas in association with defective DNA mismatch repair. The ratio of affected men to women is 2:1.

Box 18.1. Clinical Criteria for Diagnosing Lynch Syndrome

At least 3 relatives have had Lynch syndrome–related cancers[a]

At least 1 relative with colorectal cancer is a first-degree relative of 2 other affected persons

At least 2 successive generations have been affected

At least 1 relative has had colorectal cancer diagnosed before age 50 y

[a] Including cancer of the colorectum, endometrium, small bowel, ureter, or renal pelvis.

MutYH-Associated Polyposis

MYH is a DNA base excision repair enzyme. MutYH-associated polyposis (MAP) is an autosomal recessive syndrome with a wide-ranging phenotype. The colorectal adenoma burden in MAP can be similar to that in AFAP, but there are reports of patients with MAP who have more than 100 adenomas. Also, duodenal and periampullary adenomas can be found in patients with MAP, although the true incidence of upper gastrointestinal tract neoplasia is not known. Biallelic carriers, or persons with mutations in both *MYH* alleles, have an 80% cumulative risk of colorectal cancer by age 70 years, but monoallelic carriers do not appear to have an increased risk of colorectal cancer.

Hamartomatous Polyposis Syndromes

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant condition characterized by multiple hamartomatous polyps scattered throughout the gastrointestinal tract. Up to 60% of cases of the syndrome are related to germline mutations in the *LKB1* (*STK11*) gene. Melanin deposits usually can be seen around the lips, buccal mucosa, face, genitalia, hands, and feet, although occasionally the skin and intestinal lesions are inherited separately. Foci of adenomatous epithelium can develop within Peutz-Jeghers polyps and may be associated directly with an increased risk of colorectal cancer. Extracolonic malignancies include other gastrointestinal tract cancers (in the duodenum, jejunum, ileum, pancreas, biliary tree, and gallbladder), ovarian sex cord tumors, Sertoli cell testicular tumors, and breast cancer.

Tuberous Sclerosis

Tuberous sclerosis (an autosomal dominant condition) is associated with hamartomas, mental retardation, epilepsy, and adenoma sebaceum. Adenomatous polyps may occur, particularly in the distal colon.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome is an autosomal dominant condition in which juvenile mucous retention polyps (misnamed hamartomata) can arise in the colon, stomach, or elsewhere in the gastrointestinal tract. Mutations of genes in the transforming growth factor β pathway (*SMAD4, BMPR1A*, and *ENG*) have been implicated as genetic causes of the syndrome. Symptoms of bleeding or obstruction may arise during childhood and may warrant surgery on the affected intestinal segments for treatment of anemia or obstruction or for cancer prevention. The risk of colorectal cancer is increased when synchronous adenomas or mixed juvenile-adenomatous polyps are present. If prophylactic or therapeutic colonic resection is performed, ileorectostomy or total proctocolectomy should be considered because of an increased risk of recurrent juvenile polyps within the retained colorectal segment. Of note, the presence of fewer than 5 juvenile polyps (including solitary polyps) in a person with no family history of juvenile polyposis syndrome does not indicate a heritable syndrome and, on the basis of current knowledge, does not warrant further diagnostic testing or aggressive cancer surveillance.

Cowden Disease

Cowden disease is an autosomal dominant condition in which persons with *PTEN* mutations may have trichilemmomas, other skin lesions, and alimentary tract polyps that are histologically similar to the polyps of juvenile polyposis syndrome. Patients with Cowden disease are at increased risk for breast cancer (often bilateral) and papillary thyroid cancer. The risk of colorectal cancer is not well-defined in this syndrome, but colonoscopy should be included in the original diagnostic evaluation.

Cronkhite-Canada Syndrome

Cronkhite-Canada syndrome is a noninherited condition manifested by signs and symptoms of malnutrition or malabsorption. Characteristic clinical features include alopecia and hyperkeratosis of the fingernails and toenails. In the United States and Europe, Cronkhite-Canada syndrome typically develops in men, whereas in Asian countries, women appear to be affected more often. The neoplastic potential of gastrointestinal tract hamartomas in Cronkhite-Canada is uncertain; case reports of colorectal cancer in these patients suggest involvement of both typical adenomatous and serrated polyp pathways.

Prevention

Screening and Surveillance

For average-risk patients (defined as asymptomatic adults, who are 50 years or older and who do not have other known risk factors for colorectal cancer), the US Multi-Society Task Force on Colorectal Cancer has endorsed the following screening options:

- Flexible sigmoidoscopy every 5 years, *or* colonoscopy every 10 years, *or* double-contrast barium enema every 5 years, *or* CT colonography every 5 years.
- Fecal occult blood test or fecal immunochemical test every year.
- Stool DNA test (interval uncertain).

Diagnostic colonoscopy should be performed in follow-up of any screening test with positive findings.

For high-risk patients, the following recommendations have been adopted:

- FAP—flexible sigmoidoscopy at the onset of puberty for indeterminate cases.
- Lynch syndrome—colonoscopy every 1-2 years, beginning at age 20 years; it should be performed annually after age 40 years.
- Peutz-Jeghers syndrome—initial screening colonoscopy during the second decade of life, with subsequent surveillance intervals determined by examination findings.
- Strong family history of colorectal neoplasia (excluding FAP, Lynch syndrome, or other identifiable syndromes)—colonoscopy every 5 years, beginning at age 40 years (or 10 years before the youngest case diagnosis in the family, whichever is earlier). For patients with 1 first-degree relative who received a diagnosis at age 60 years or older or 2 second-degree relatives with colorectal cancer diagnosed at any age, any of the endorsed screening options may be selected, beginning at age 40 years (rather than age 50 years for average-risk patients).
- Inflammatory bowel disease—annual colonoscopy with surveillance biopsies, beginning 8-10 years after the onset of colitis or annually after the diagnosis of primary sclerosing cholangitis.

History of Colorectal Neoplasia

After a complete clearing colonoscopy (ie, the bowel preparation was adequate and all colonic polyps were removed), subsequent examinations can be delayed for patients who have 1 or 2 tubular adenomas that are smaller than 1 cm and have low-grade dysplasia at baseline. Surveillance colonoscopy is indicated at 3 years for patients with advanced adenomas or 3 to 10 adenomas at baseline. Family history should be considered on a case-by-case basis when determining postpolypectomy surveillance intervals. Patients with more than 10 adenomas at a single examination should have colonoscopy again in less than 3 years. Patients with large (>2 cm), sessile adenomas that are removed piecemeal should have endoscopy repeated in 2 to 6 months. Residual adenomatous tissue after 2 or 3 therapeutic colonoscopies should prompt surgical consultation. The natural history of sessile serrated adenomas and large proximal hyperplastic polyps is not fully understood; surveillance intervals recently proposed by an expert panel are similar to those for adenomatous polyps by size, number, and advanced histologic features.

Malignant polyps, defined as neoplasms with dysplastic cells invading through the muscularis mucosa, can be treated endoscopically if 1) the lesion has been excised completely and fully examined by a pathologist; 2) the depth of invasion, grade of differentiation, and completeness of excision can be determined accurately; 3) poor differentiation, vascular invasion, and lymphatic involvement are not present; and 4) the margin of excision is free of cancer cells. Follow-up colonoscopy should be performed at 3 months for malignant polyps that meet these favorable prognostic criteria.

Patients with potentially curable colon or rectal cancer should have a clearing colonoscopy preoperatively or within 3 to 6 months postoperatively if obstructive lesions prevented preoperative colonoscopy. After clearing colonoscopy, subsequent surveillance examinations can be performed at 1 year, 3 years, and 5 years if no additional colorectal neoplasia is found.

Chemoprevention

Chemoprevention is the use of chemical compounds to prevent, inhibit, or reverse carcinogenesis before the invasion of dysplastic epithelial cells across the basement membrane. In its broadest sense, chemoprevention includes both nutritional and pharmaceutical interventions. With regard to pharmaceutical agents, nonsteroidal antiinflammatory drugs are structurally diverse, yet they appear to share abilities to decrease proliferation, slow cell cycle progression, and stimulate apoptosis. Extensive epidemiologic data uphold a negative risk (40%-60%) association between the regular use of nonsteroidal antiinflammatory drugs and colorectal tumors. The chemopreventive effects of these drugs are thought to be derived through cyclooxygenase 2 (COX-2) inhibition. In several large clinical trials, agents that selectively block this enzyme isoform (celecoxib and rofecoxib) have been shown to decrease the recurrence rates of adenoma. However, selective COX-2 inhibitors have been associated also with increased cardiovascular toxicity, which has limited their chemopreventive applications to high-risk clinical settings (such as adjunct therapy for FAP).

Treatment of Colon Cancer

For most patients who have colon cancer, in the absence of known distant metastases or prohibitive comorbid conditions, surgical excision is the initial treatment. Typical operations for colon cancer include segmental resection. The procedures can be performed through an open incision or laparoscopically, if technically feasible. More extensive operations can be performed, such as subtotal colectomy for patients who have colorectal neoplasia

in multiple colonic segments or proctocolectomy for patients who have familial cancer syndromes. Operative intervention also may be considered for selected patients who have isolated liver or lung metastases. For surgically incurable patients, resection of the primary cancer is usually indicated only if there is bleeding, obstruction, or impending obstruction. Postoperative, or adjuvant, cytotoxic chemotherapy is recommended for patients with stage III colon cancer. It should be considered also for patients with stage II colon cancer who have poor prognostic factors, as based on pathology review. The preferred regimen is FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) for 6 months.

Adenocarcinomas in the middle and upper rectum usually are removed by anterior resection, with colorectal anastomosis. Cancers in the lower rectum (0-5 cm above the anal verge) often require abdominoperineal resection, with a permanent colostomy, although anterior resection with low coloanal anastomosis may be considered for some patients. Preoperative, or neoadjuvant, treatment with 5-fluorouracil–based chemotherapy in combination with radiotherapy generally is indicated for patients with tumors that are staged with CT and endoscopic ultrasonography as T3 and higher or N1 and higher. Adjuvant chemotherapy with 5-fluorouracil and leucovorin (with or without oxaliplatin) is recommended for patients with stage II or stage III rectal cancer. For palliation of metastatic disease, both FOLFOX and FOLFIRI (a regimen containing irinotecan in place of oxaliplatin) are accepted as first-line cytotoxic regimens. Molecularly targeted therapies have shown benefits for subsets of patients with metastatic colorectal cancer. Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), impairing the proliferation of endothelial cells and formation of new blood vessels. Cetuximab and panitumumab are monoclonal antibodies that target epidermal growth factor receptor (EGFR). *KRAS* tumor testing is used to select which patients will respond best to an EGFR inhibitor, which may improve outcomes for patients with advanced tumors with wild-type *KRAS*. Mutant *KRAS* constitutively activates the RAS-RAF-ERK pathway downstream from EGFR, resulting in resistance to anti-EGFR therapy.

Suggested Reading

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19

Irritable Bowel Syndrome[a]

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Irritable bowel syndrome (IBS) is a common condition that contributes substantially to health care costs. It is a chronic gastrointestinal tract disorder of unknown etiology characterized by abdominal pain and altered bowel habits in the absence of detectable biochemical or structural abnormalities. Treatment of IBS is symptom based. However, recent discoveries in the physiology of the enteric nervous system, the gut-brain axis, and the intestinal flora have led to the development of therapies targeted at potential pathophysiologic mechanisms of IBS. In addition, the role of psychologic issues has been well recognized, and behavioral interventional therapies are important. The overall goal with IBS therapy is to improve the patient's symptoms and quality of life and, ideally, to prevent the suffering that patients experience.

Definition

The symptom criteria for IBS are listed in Box 19.1. The Rome criteria were developed in conjunction with the World Congress of Gastroenterology held in Rome, Italy, in 1988 and were revised (Rome II) in 1999 and again in 2006 (Rome III). The Rome criteria are similar to the criteria established by Manning and colleagues in 1978. However, with the Rome criteria, the goal was to incorporate constipation-type symptoms into the definition of IBS.

As with any set of criteria, there is a trade-off between sensitivity and specificity, depending on the threshold used. In clinical practice, this can be helpful. The more criteria a particular patient meets, the more likely the patient is to have IBS. Nonetheless, the diagnosis of IBS can be made only in the absence of structural or biochemical abnormalities that would explain the symptoms.

Epidemiology

IBS is a common condition, affecting 10% to 20% of the population in developed countries. Although many studies have assessed the prevalence of IBS, data on incidence are more difficult to obtain. Because not everyone with IBS seeks medical care, data on incidence would need to come from a population-based study. The exact number varies, but about 10% of the general population reports the onset of symptoms of IBS over a 1-year period. However, it is not known whether these people had the syndrome in the past. Thus, this is an onset rate rather than a true incidence rate. Approximately one-third of persons with IBS report that symptoms resolve over time. One estimate of the incidence of clinically diagnosed IBS is 196 per 100,000 person-years. This clinical incidence figure is lower than the 10% onset figure, which likely reflects both the fluctuating pattern of symptoms and the limited use of health care by some persons with IBS. Still, this is much higher than the incidence of colon cancer (50 per 100,000 person-years) and inflammatory bowel disease (10 per 100,000 person-years).

Risk Factors

Multiple risk factors have been proposed for IBS. In clinic-based studies, there is a strong association with sex. However, the

[a] Portions of this chapter were adapted from Locke GR III. Natural history of irritable bowel syndrome and durability of the diagnosis. Rev Gastroenterol Disord. 2003;3 Suppl 3:S12-7 and Camilleri M. Peripheral mechanisms in irritable bowel syndrome. N Engl J Med. 2012 Oct 25;367(17):1626-35. Used with permission.

Abbreviations: FDA, US Food and Drug Administration; FGF-19, fibroblast growth factor 19; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, irritable bowel syndrome; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant

Box 19.1. Diagnostic Criteria for Irritable Bowel Syndrome[a]

Recurrent abdominal pain or discomfort[b] ≥3 d monthly in the past 3 mo and associated with ≥2 of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

[a] Criteria fulfilled for the past 3 months, with symptom onset at least 6 months before diagnosis.

[b] *Discomfort* means an uncomfortable sensation not described as pain.

Adapted from Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006 Apr;130(5):1480-91. Erratum in: Gastroenterology. 2006 Aug;131(2):688. Used with permission.

female to male ratio in the community is approximately 2:1. Thus, sex may have a role not only in the onset of IBS but also in health care–seeking behavior. Even though the prevalence of IBS decreases slightly with age, new symptoms may occur in the elderly. Prevalence estimates are available from around the world, but no consistent racial or ethnic differences have been identified.

Multiple studies have assessed the role of personality characteristics, psychiatric illness, and physical and sexual abuse in the development of IBS. These problems are common in patients with IBS evaluated in academic medical centers. However, persons in the community who have IBS are much less distressed.

Many patients with IBS report that a family member also has the condition. Familial aggregation of IBS exists, and twin studies have suggested a genetic component. Other studies, though, have shown that seeking health care for gastrointestinal problems is increased among children of parents with gastrointestinal symptoms. Additional study is needed to distinguish between nature and nurture in the development of IBS.

Postinfectious IBS is a well-recognized subtype of IBS that develops de novo after bacterial or viral gastroenteritis. The propensity for postinfectious IBS to develop is associated with female sex, duration of illness, and the psychologic state (anxiety and depression) of the person at the time of infection. It usually develops into a diarrhea-predominant phenotype. The explanation for the persistence of elevated intestinal inflammatory markers in individuals with postinfectious IBS is an area of active investigation.

Food allergies or sensitivities also may have a role in the development of IBS. Patients with IBS symptoms report more sensitivity to food than people without symptoms. However, the data on exclusion diets have not convincingly shown that food is a cause of the symptoms.

Pathogenesis

The cause of IBS is unknown. Multiple models of pathophysiology include altered motility, visceral hypersensitivity, abnormal brain-gut interaction, autonomic dysfunction, and immune activation. In the past, the predominant pathophysiologic mechanisms in IBS were perceived to be abnormalities intrinsic to the smooth muscle of the gut, visceral hypersensitivity, and psychologic stress. However, several specific peripheral mechanisms that perturb motor and sensory functions result in symptoms of IBS, including abnormal colonic transit and rectal evacuation; intraluminal intestinal irritants, such as maldigested carbohydrates or fats, an excess of bile acids, and gluten intolerance; altered bile acid synthesis; and alterations in the intestinal microbiome.

Slow colonic transit occurs in 25% of patients with constipation-predominant IBS. Disorders of rectal evacuation, such as dyssynergic defecation and descending perineum syndrome, may mimic symptoms of constipation-predominant IBS and are important to consider.

Diarrhea-predominant IBS is associated with rapid colon transit in up to 45% of patients. Disorders that mimic diarrhea-predominant IBS include food intolerances, disaccharidase deficiencies, celiac disease, microscopic colitis, gluten intolerance without celiac disease, and idiopathic bile acid malabsorption.

There is an association of ingestion of food with the induction of gastrointestinal symptoms in IBS. The fat content of the meal appears to have a key role in provoking gastrointestinal symptoms in IBS by inducing high-amplitude colonic contractions. In addition, ingestion of poorly absorbed, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) may induce symptoms of IBS. There may be a higher prevalence of celiac disease among patients with IBS. Furthermore, gluten is associated with symptoms of IBS, and celiac disease–free patients with IBS who have the HLA-DQ2 or HLA-DQ8 genotypes are more likely to respond to gluten withdrawal than patients without these genotypes. Therefore, dietary manipulation with a low-FODMAP and gluten-free diet is a potentially therapeutic option for patients with IBS.

Bile acid malabsorption occurs in 25% of cases of diarrhea-predominant IBS. Cholerheic diarrhea, from excess intracolonic bile acids in IBS, results from derangements in the enterohepatic circulation of bile acids. The suggested mechanism for the excess intracolonic bile acids in IBS is deficiency in ileal secretion of fibroblast growth factor 19 (FGF-19). FGF-19 is a hormone produced by ileal enterocytes in response to bile acids and is secreted into the portal circulation, where it suppresses bile acid synthesis by the liver. The ileal production of FGF-19 is reduced in diarrhea-predominant IBS, resulting in excessive synthesis of bile acids, which then overwhelms ileal absorptive capacity and leads to bile acid diarrhea.

Alterations in the intestinal microbiome may be a relevant pathophysiologic mechanism in IBS. Small intestinal bacterial overgrowth may be the cause of IBS symptoms. In randomized controlled trials, the minimally absorbed antibiotic rifaximin provided significant relief of bloating, abdominal pain, and watery stools. However, the mechanism underlying the beneficial effect of rifaximin on symptoms of IBS is controversial. It is unclear whether IBS symptoms improve with poorly absorbed antibiotics because of treatment of small intestinal bacterial overgrowth or because of a decreased colonic bacterial load with reduction in bacterial fermentation. Neither rifaximin nor any other antibiotic has been approved for treatment of IBS.

Diagnosis

The diagnosis of IBS is made on the basis of symptom criteria (Box 19.1) in the absence of structural or biochemical abnormalities that can explain the symptoms. Many disorders can cause abdominal pain. However, the combination of abdominal pain and abnormal defecation has a more limited differential diagnosis. Colon cancer, inflammatory bowel disease, thyroid disorders, celiac disease, bacterial overgrowth, and giardiasis are all

relatively common conditions that can cause similar symptoms. Carcinoid syndrome, microscopic colitis, and eosinophilic gastroenteritis also can cause similar symptoms, but these conditions are less common. IBS is so common that it is difficult to justify performing extensive diagnostic tests on a large proportion of the population since all the tests have a very low yield.

Young patients with classic symptoms of IBS do not necessarily need any tests when they present to their primary care provider. Simple blood tests, stool tests for ova and parasites and occult blood, and an anatomical evaluation of the colon may be considered (Figure 19.1). Patients older than 50 years need a full colonic evaluation to exclude colorectal cancer. Several studies have shown an increased prevalence of celiac disease among patients with diarrhea-predominant IBS, and routine serologic screening for celiac disease in patients with diarrhea-predominant IBS is recommended.

Prognosis

The natural history of IBS is becoming better understood. In approximately 30% of patients, the symptoms resolve over the course of a year. This contributes to the placebo response rate, which has made evaluation of investigative agents difficult. Although IBS symptoms may resolve, symptoms of another functional gastrointestinal disorder develop in some patients. Thus, the degree to which the gastrointestinal symptoms resolve completely is not clear. A pattern of the condition coming, going, and changing over time is quite common.

Management

Although IBS often is managed with a high-fiber diet and antispasmodic agents, an approach that considers the patient's predominant symptom is recommended (Figure 19.1). Does the patient complain primarily of constipation, diarrhea, or abdominal pain? Constipation can be treated with laxatives and a high-fiber diet, and diarrhea may be treated with loperamide, especially when taken before meals. A diet high in soluble fiber (eg, psyllium, also called ispaghula) rather than insoluble fiber (eg, wheat bran) may improve global symptoms and constipation in IBS with variable effects on abdominal pain.

Antispasmodic agents (eg, hyoscine and peppermint oil) are appropriate for patients who have primarily abdominal pain and may provide short-term relief of abdominal discomfort. These agents have been prescribed because of the belief that the pathophysiologic mechanism of IBS is intestinal spasms and irregular

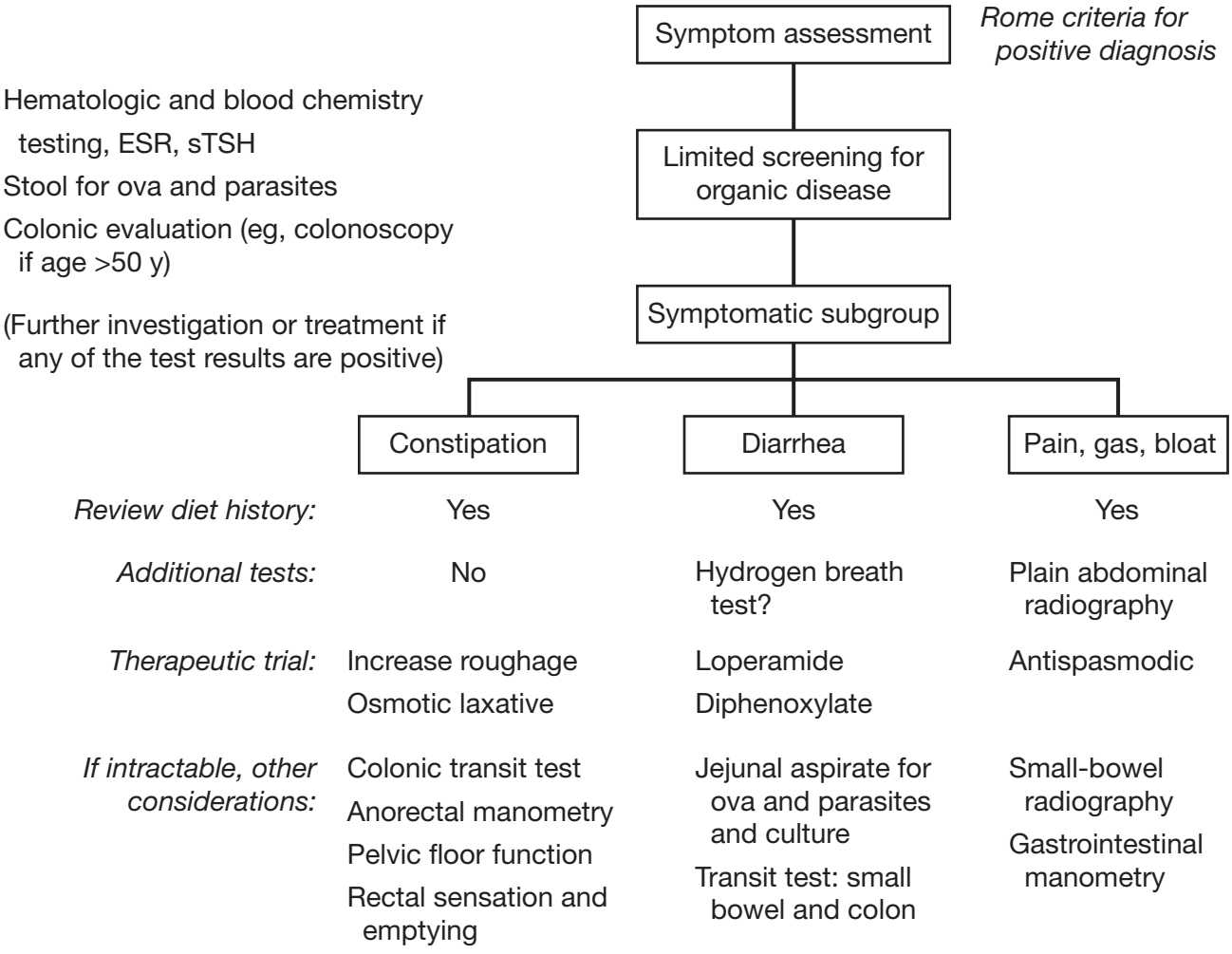

Figure 19.1. Management of Irritable Bowel Syndrome. ESR indicates erythrocyte sedimentation rate; sTSH, sensitive thyrotropin. (Adapted from Drossman MA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. Gastroenterology. 1997 Jun;112[6]:2120-37. Used with permission.)

contractility. The clinical trial data on the effectiveness of antispasmodic agents are mixed. However, with the absence of alternative medications, antispasmodic agents have been used widely. In each case, a dietary history is important to ensure that the patient is not consuming products that may inadvertently cause diarrhea, constipation, or abdominal gas. Further evaluation should be withheld until the initial treatment program is undertaken (3-6 weeks).

The hope is that the patient will be reassured about the diagnosis and will have a response to the initial therapy. However, some patients continue to have pronounced symptoms and seek care. What are the options for these patients? For constipation, therapy typically is laxatives. Further testing and treatment are based on the predominant symptom. Patients with refractory constipation need to be evaluated for problems of colonic transit and pelvic floor dysfunction (see Chapter 20, "Constipation and Disorders of Pelvic Floor Function"). Patients with pelvic floor dysfunction may benefit from biofeedback.

Patients with documented delay in colonic transit may be considered for colonic resection. However, if the patient has symptoms of IBS, surgery for colonic inertia needs to be considered carefully because the abdominal pain may persist postoperatively. Various laxatives and intestinal secretagogues are available for treating IBS and constipation. Laxatives include osmotic agents and stimulant products. The 4 main types of osmotic laxatives are polyethylene glycol–based solutions, magnesium citrate-based products, sodium phosphate-based products, and nonabsorbable carbohydrates (lactulose, sorbitol). These hypertonic agents draw fluid into the intestinal lumen by osmosis and cause diarrhea. Stimulant laxatives (eg, bisacodyl, glycerin suppositories) induce high-amplitude propagated colonic contractions and appear to be safe even with long-term use. Stimulant laxatives are best used as rescue agents when the patient has not had a bowel movement for several days. Lubiprostone and linaclotide are 2 intestinal secretagogues that are approved by the US Food and Drug Administration (FDA) for treating constipation in IBS. By stimulating a net efflux of ions and water into the intestinal lumen, these secretagogues accelerate transit and facilitate defecation. Lubiprostone is a bicyclic fatty acid derivative of prostaglandin E_1 that works mainly by activating apical type 2 chloride channels. It is approved for treatment of IBS with constipation in women at a dose of 8 mcg twice daily. Nausea is the main side effect of lubiprostone and may be lessened by ingestion with food. Linaclotide is a guanylate cyclase-C agonist that activates these receptors on intestinal mucosa cells, which leads to the opening of cystic fibrosis transmembrane regulator chloride channels. Linaclotide is FDA approved for treating IBS with constipation at a dose of 290 mcg daily.

Tests to consider for patients with diarrhea include stool chemistry tests for surreptitious laxative abuse, duodenal aspirate or hydrogen breath testing for bacterial overgrowth, colonic biopsies for microscopic colitis, determination of urinary 5-hydroxyindoleacetic acid for carcinoid syndrome, and a small-bowel colonic transit study. The yield of these tests is low, but they are useful for evaluating patients who have chronic diarrhea with increased stool volume. Treatment with high-dose loperamide (up to 16 mg daily), cholestyramine, clonidine, verapamil, or octreotide may be considered. Most of these treatments are off-label use. The serotonin receptor antagonist alosetron is effective at relieving global symptoms in male and female IBS patients who have diarrhea that has not responded to conventional therapies. The potential risk of ischemic colitis has led to a restricted prescription program for alosetron.

Pain-predominant IBS can be a management challenge. A plain radiograph of the abdomen obtained during a time of severe pain may help to exclude obstruction. In academic medical centers, pseudo-obstruction or other motility disorders may be evaluated, but pain is not common in these conditions. Often, the next step is a course of treatment with a low dose of a tricyclic antidepressant. The goal is not to alleviate depression but rather to reduce visceral sensation.

Some patients with IBS report bloating as the major symptom. Studies have reported some benefit with probiotics, particularly bifidobacteria.

The association between psychologic distress and IBS is well established. When formal psychiatric disorders are present, appropriate therapy directed toward treating the underlying disorder is mandatory. Even when there is no diagnosis of a psychiatric disorder, the approach of using psychologic intervention is helpful in the management of IBS. When traditional symptomatic measures have not been adequate, treatment with low doses of tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) are effective at relieving global IBS symptoms and reducing abdominal pain. The effects of TCAs on the gastrointestinal tract differ from those of SSRIs. TCAs prolong orocecal and whole gut transit times, whereas SSRIs decrease orocecal and whole gut transit times. Therefore, TCAs may work better in IBS with diarrhea, and SSRIs may be better tolerated in IBS with constipation. Cognitive behavior therapy, dynamic psychotherapy, and hypnotherapy are effective psychologic therapies in the management of IBS. In addition, patients with IBS may benefit from formal pain management approaches.

Health Care Use

Annually, IBS accounts for 3.5 million physician visits, 2.2 million prescriptions, and 35,000 hospitalizations. Primary care physicians provide most care for patients with IBS, although a survey of gastroenterologists indicated that 28% of their patient population had IBS. The exact expenditures accountable to IBS are difficult to determine. In 1 study, patients with IBS in the community were found to incur an extra $300 annually in health care expenditures. Extrapolated to the US population, this expense is equal to $8 billion. Also, IBS is associated with absenteeism. This and other indirect costs to patients and their families make the total cost of IBS considerable.

Summary

IBS symptoms may result from several specific peripheral mechanisms, including rectal evacuation disorders, intraluminal intestinal irritants, and alterations in the microbiome. Diagnosis of IBS is based on symptoms in the absence of structural or biochemical abnormalities. Routine serologic screening for celiac disease in patients with diarrhea-predominant IBS is recommended. Initial treatment involves lifestyle and dietary modifications with symptomatic remedies. Patients with persistent gastrointestinal symptoms despite these initial measures should undergo tests to identify causative factors.

Suggested Reading

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20

Constipation and Disorders of Pelvic Floor Function[a]

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Colonic Motor Physiology and Pathophysiology: Salient Aspects

Function

Colonic functions include absorption of water and electrolytes, storage of intraluminal contents until elimination is socially convenient, and nutrient salvage from bacterial metabolism of carbohydrates that are not absorbed in the small intestine. The colon absorbs all but 100 mL of fluid and 1 mEq of sodium and chloride from approximately 1,500 mL of chyme received over 24 hours. Absorptive capacity can increase to 5 to 6 L of fluid and to 800 to 1,000 mEq of sodium and chloride daily. In healthy people, the average mouth-to-cecum transit time is approximately 6 hours, and average regional transit times through the right, left, and sigmoid colon are about 12 hours each, with an average total colonic transit time of 36 hours. (The physiology of defecation is discussed below in the Disorders of Pelvic Floor Function section.)

Regional Differences in Colonic Motor Function

The right colon is a reservoir that mixes and stores contents and absorbs fluid and electrolytes. The left colon is primarily a conduit, whereas the rectum and anal canal are responsible for continence and defecation. The ileocolic sphincter regulates the intermittent transfer of ileal contents into the colon, a process that normalizes in response to augmented storage capacity in the residual transverse and descending colon within 6 months after right hemicolectomy.

Motor Patterns

Colonic motor activity is extremely irregular, ranging from being quiescent (particularly at night) to having isolated contractions, bursts of contractions, or propagated contractions. In contrast to the small intestine, the colon does not have rhythmic migrating motor complexes. Contractions are *tonic* or sustained, lasting several minutes to hours, and shorter or *phasic*. *Propagated phasic contractions* propel colonic contents over longer distances than *nonpropagated phasic contractions*. *High-amplitude propagated contractions* are more than 75 mm Hg in amplitude, occur about 6 times daily (frequently after awakening and after meals), are responsible for mass movement of colonic contents, and frequently precede defecation. Stimulant laxatives such as bisacodyl (Dulcolax) and glycerol induce high-amplitude propagated contractions.

Colonic Contractile Response to a Meal

Neurohormonal mechanisms are responsible for increased colonic motor activity beginning within a few minutes after ingestion of a meal of 500 kcal or more. The term *gastrocolic reflex* is a misnomer because this response, induced by gastric distention and chemical stimulation by nutrients, is observed

[a] Portions of this chapter have been adapted from Bharucha AE. Fecal incontinence. Gastroenterology. 2003;124(6):1672-85; Bharucha AE. Treatment of severe and intractable constipation. Curr Treat Options Gastroenterol. 2004;7(4):291-8; and Bharucha AE, Philips SF. Slow-transit constipation. Curr Treat Options Gastroenterol. 2001;4;309-15. Used with permission.

Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); IBAT, ileal bile acid transporter; MR, magnetic resonance; MRI, magnetic resonance imaging; PNTML, pudendal nerve terminal motor latency

even after gastrectomy. This response may explain postprandial urgency and abdominal discomfort in patients with irritable bowel syndrome.

Colonic Relaxation

Colonic relaxation resulting from sympathetic stimulation or opiates may cause acute colonic pseudo-obstruction, or Ogilvie syndrome. Stimulation of α_2-adrenergic receptors decreases the release of acetylcholine from excitatory cholinergic terminals in the myenteric plexus, thereby inhibiting gastrointestinal motility. Conversely, reduced tonic inhibition of the sympathetic system impairs the net absorption of water and electrolytes and accelerates transit in patients who have diabetic neuropathy, thus resulting in diarrhea. Clonidine restores the sympathetic brake, reducing diarrhea.

Colocolonic Inhibitory Reflexes

Peristalsis is a local reflex mediated by intrinsic nerve pathways and characterized by contraction proximal to the distended segment and relaxation distal to it. In addition, rectal or colonic distention can inhibit motor activity in the stomach, small intestine, or colon. These inhibitory reflexes are mediated by extrinsic reflex pathways with synapses in the prevertebral ganglia, independent of the central nervous system. They may account for delayed left colonic transit or small intestinal transit (or both) in patients with obstructive defecation.

Serotonin and the Gut

About 95% of the body's serotonin (5-hydroxytryptamine [5-HT]), a monoamine neurotransmitter, is in the gut: 90% in enterochromaffin cells and 10% in enteric neurons. The effects of serotonin are mediated by receptors located on gut neurons, smooth muscle, and enterochromaffin cells. There are a number of families of 5-HT receptors. The 5-HT_3 and 5-HT_4 receptors and, to a lesser degree, 5-HT_{1p}, 5-HT_{1a}, and 5-HT_2 receptors are important targets of pharmacologic modulation in the gut. Cisapride, prucalopride, and tegaserod maleate (Zelnorm) are 5-HT_4 receptor agonists. Alosetron and cilansetron are more potent 5-HT_3 receptor antagonists than ondansetron. The 5-HT receptors have motor and sensory effects.

Motor

Stimulation of serotoninergic 5-HT_4 receptors facilitates both components of the peristaltic reflex (ie, proximal excitation coordinated with distal inhibition). Thus, stimulation of 5-HT_4 receptors located on cholinergic enteric neurons induces the release of acetylcholine and enhances contractility, whereas 5-HT_4 receptor–mediated stimulation of inhibitory neurons releases inhibitory neurotransmitters (eg, nitric oxide or vasoactive intestinal polypeptide), which relax smooth muscle.

Sensory

Receptors for 5-HT_3 and 5-HT_4 are located on intrinsic primary afferent neurons, which initiate peristaltic and secretory reflexes. The 5-HT_3 receptors are located also on extrinsic sensory afferents and vagal afferents, which partly explains why 5-HT_3 antagonists reduce nausea.

Assessment of Colonic Transit

Colonic transit can be measured with commercially available radiopaque markers (Sitzmark capsule), scintigraphy, or a wireless pH-pressure capsule. These techniques entail counting the number of orally ingested markers that remain in the colon as seen on plain radiographs of the abdomen. One approach is to administer a capsule containing 20 markers on day 1. Delayed colonic transit is manifested by 8 or more markers seen on plain films on day 3 or by 5 or more markers seen on day 5.

With scintigraphy, the isotope (generally, technetium Tc 99m or indium In 111) is delivered into the colon by orocecal intubation or within a delayed-release capsule. The delayed-release capsule contains radiolabeled activated charcoal covered with a pH-sensitive polymer (methacrylate) designed to dissolve in the alkaline pH of the distal ileum. This releases the radioisotope within the ascending colon. Gamma camera scans taken 4, 24, and, if necessary, 48 hours after ingestion of the isotope show the colonic distribution of isotope. Regions of interest are drawn around the ascending, transverse, descending, and sigmoid colon combined with the rectum; counts in these areas are weighted by factors of 1 through 4, respectively, and stool counts are weighted by a factor of 5. Thus, colonic transit may be summarized as an overall geometric center (Figure 20.1). The 4-hour scan identifies rapid colonic transit, and the 24-hour and 48-hour scans show slow colonic transit. Assessments of colonic transit made with

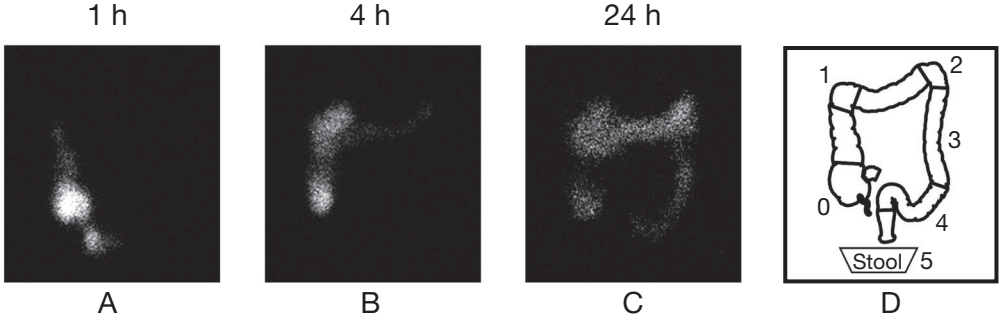

Figure 20.1. Scintigraphic Assessment of Colonic Transit Showing Isotope Progression. A, Cecum and ascending colon (1 hour). B, Ascending and transverse colon (4 hours). C, Ascending, transverse, descending, and rectosigmoid colon (24 hours). D, Numbers represent the average isotope distribution corresponding to a geometric center of 1 to 5. In this patient, the geometric center at 24 hours was 2.2 (reference range, 1.6-3.8). (Data from Bharucha AE, Klingele CJ. Autonomic and somatic systems to the anorectum and pelvic floor. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Vol 1. 4th ed. Philadelphia [PA]: Elsevier Saunders; c2005. p. 279-98.)

radiopaque markers, scintigraphy, and the pH-pressure capsule are comparable. The radiopaque marker technique is simpler and more widely available. However, with scintigraphy, colonic transit can be assessed in 48 hours, compared with 5 to 7 days for radiopaque markers. Moreover, gastric, small intestinal, and colonic transit can be assessed simultaneously with scintigraphy.

Constipation

Definition

A committee of experts developed symptom-based criteria (the Rome criteria) for diagnosing functional gastrointestinal disorders. These criteria are essential for clinical trials and research studies but are also useful in clinical practice. By convention, these symptom criteria need to be present for at least 3 months, with total symptom duration of 6 months or more.

Functional constipation is defined by 2 or more of the following symptoms: 1) fewer than 3 defecations weekly, 2) straining, 3) lumpy or hard stools, 4) sensation of incomplete evacuations, 5) sensation of anorectal obstruction or blockage, and 6) manual maneuvers to facilitate defecation. For symptoms 2 through 6 to be considered present, they should occur with one-fourth of defecations.

Constipation-predominant irritable bowel syndrome is defined by abdominal discomfort and at least 2 of the following 3 symptoms: 1) abdominal discomfort associated with change in stool form, 2) abdominal discomfort associated with change in stool frequency, and 3) abdominal discomfort relieved by defecation.

Clinical Assessment

Clinical assessment should focus on identifying 1) secondary causes of constipation (Boxes 20.1 and 20.2); 2) inadequate dietary intake of calories and fiber; 3) a history of physical, emotional, or sexual abuse; and 4) obstructive defecation. Bowel diaries are more accurate than self-reporting for characterizing bowel habits, particularly stool frequency. Extremes of stool form, characterized by the Bristol stool form scale, correlate strongly with delayed colonic transit (hard, small pebbles) and accelerated colonic transit (watery stools). In contrast to stool frequency recorded in diaries, frequency based on recall alone does not correlate with colonic transit. Certain symptoms (prolonged straining, sense of anorectal blockage, a tendency to facilitate defecation by assuming different positions, difficulty in evacuating soft stool, and digital maneuvers to facilitate defecation) are suggestive but not diagnostic of functional defecatory disorders. The examination may demonstrate anismus, inadequate perineal descent, or, conversely, ballooning of the perineum with excessive descent.

Box 20.1. Common Secondary Causes of Constipation

- Structural—colonic or anorectal (eg, colon cancer or stricture, large rectocele)
- Endocrine—diabetes mellitus, hypothyroidism
- Metabolic—hypokalemia, hypercalcemia, hypocalcemia, uremia
- Infiltrative—scleroderma, amyloidosis
- Neurologic—Parkinson disease, spinal cord disease, autonomic neuropathy, multiple sclerosis
- Psychologic—anorexia nervosa

Box 20.2. Common Medications That Cause Constipation

- Analgesics—opiates, nonsteroidal antiinflammatory drugs
- Antihypertensives—calcium channel blockers, α_2-agonists, diuretics (low potassium level)
- Antacids containing aluminum, calcium
- Anticholinergics, antidepressants, antihistamines, antiparkinsonian agents
- Long-term laxative use
- Others—iron, cholestyramine

Practical Classification of Constipation

A practical approach to classifying and managing chronic constipation is shown in Figure 20.2. After secondary causes of constipation are excluded, anorectal functions should be assessed in patients with constipation that does not respond to dietary fiber supplementation or over-the-counter laxatives (or both). Anorectal tests are necessary because symptoms alone cannot distinguish between constipation resulting from defecatory disorders, normal transit, and slow transit. Defecatory disorders, which are characterized by symptoms of constipation and anorectal test results indicative of disordered defecation, should be managed primarily by pelvic floor retraining (biofeedback therapy). When anorectal test results are normal, colonic transit should be assessed to distinguish normal- from slow-transit constipation. When anorectal test results are abnormal (ie, they indicate a defecatory disorder), it is not essential to evaluate colonic transit before biofeedback therapy because the management is the same, regardless of whether colonic transit is normal or slow; 50% of patients with defecatory disorder have slow colonic transit. However, colonic transit should be evaluated in patients with defecatory disorder who do not respond to biofeedback therapy.

Normal-transit constipation includes irritable bowel syndrome and functional constipation. In irritable bowel syndrome, abdominal pain is associated with defecation or a change in bowel habits (ie, harder or less frequent stools). Patients with functional constipation also may have abdominal pain, but by definition the pain is not relieved by defecation or associated temporally with harder or less frequent stools. Most patients with defecatory disorder also have delayed colonic transit. Consequently, delayed colonic transit does not imply slow-transit constipation.

Colonic inertia refers to severe colonic motor dysfunction that is identified by reduced colonic contractile responses to a meal and stimulants such as bisacodyl or neostigmine, as assessed with intraluminal measurements of pressure activity or tone.

Management of Constipation

Principles

Reassurance and education about normal bowel habits, the need for adequate caloric intake and dietary fiber supplementation, and the absence of a "serious disorder" are vital. Deficient caloric

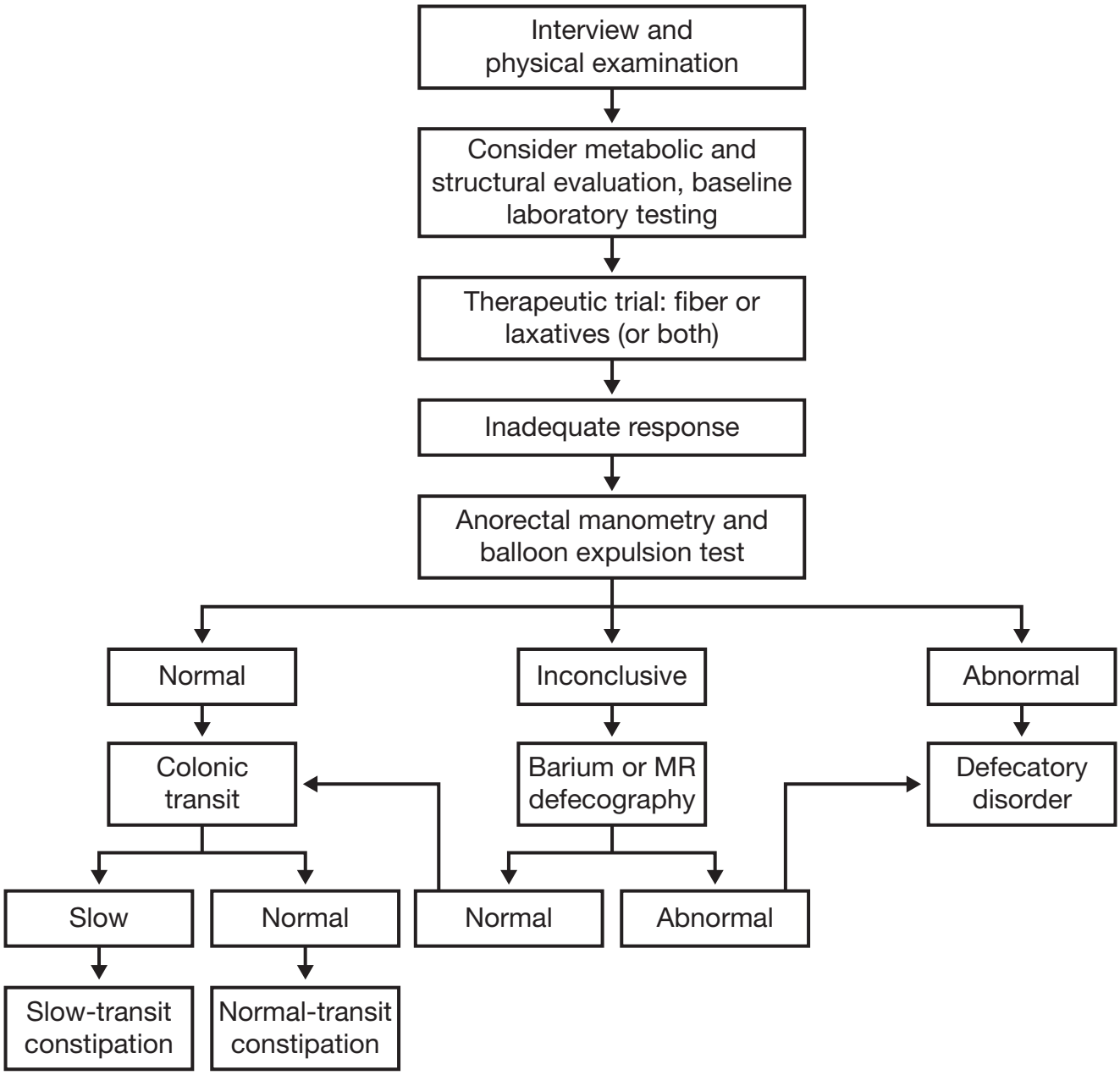

Figure 20.2. Approach for Classifying and Managing Chronic Constipation. MR indicates magnetic resonance. (Adapted from Bharucha AE, Dorn SD, Lembo A, Pressman A; American Gastroenterological Association. American Gastroenterological Association medical position statement on constipation. Gastroenterology. 2013 Jan;144[1]:211-7. Used with permission.)

intake can cause or exacerbate constipation, whereas refeeding may restore colonic transit.

Medical Therapy

A stepwise approach that begins with dietary fiber supplementation and osmotic or stimulant laxatives should be used to manage constipation. These agents are relatively safe, inexpensive, and widely used, and, in many cases, efficacy has been proved in controlled trials. Further testing is warranted for patients who do not respond to these agents. This evaluation should be considered earlier if defecatory disorders are strongly suspected clinically. For normal-transit and slow-transit constipation, treatment with laxatives or a secretagogue (ie, lubiprostone), or both, should be considered.

Increasing dietary fiber with either food or a fiber supplement increases stool weight and accelerates colonic transit. Fiber intake should be increased gradually to 12 to 15 g daily: psyllium (Konsyl, Metamucil), daily with fluid, or methylcellulose (Citrucel), 1 teaspoon up to 3 times daily; Konsyl, 2 teaspoons twice daily; calcium polycarbophil (FiberCon), 2 to 4 tablets daily; or bran, 1 cup daily. Fiber supplements are more effective in normal-transit or "fiber-deficiency" constipation (80% of patients have a symptomatic response) than in slow-transit constipation or pelvic floor dysfunction. Fiber supplementation should start at a small dose administered twice daily (morning and evening) with fluids or meals, with the dose increasing gradually after 7 to 10 days. Patients should be reassured that although fiber supplements may increase gaseousness, this often subsides with time.

A response to fiber supplements is evident over several weeks, not days as with a laxative. Bloating may be reduced by gradually titrating the dose of dietary fiber to the recommended dose or by switching to a synthetic fiber preparation such as methylcellulose. Bran impairs absorption of iron and calcium. Fiber supplements are contraindicated for patients with intestinal obstruction, fecal impaction, or severe vomiting.

- Dietary fiber content should be increased gradually to 12-15 g daily for patients with constipation.
- In normal-transit constipation, 80% of patients have a symptomatic response to dietary fiber supplementation.

Hyperosmolar agents (sorbitol or lactulose, 15-30 mL once or twice daily) are nonabsorbable disaccharides metabolized by colonic bacteria into acetic and other short-chain fatty acids. Sorbitol and lactulose accelerate proximal colonic transit in healthy people. Both agents may cause transient abdominal cramps and flatulence. They are equally effective for treating constipation in the elderly. However, lactulose is extremely sweet and more expensive than sorbitol. A controlled study showed that polyethylene glycol (MiraLAX), 17 g daily for 6 months, is superior to placebo for improving symptoms in chronic constipation. Oral sodium phosphate solution is used for bowel cleansing, occasionally by patients with severe constipation. However, acute phosphate nephropathy (acute nephrocalcinosis), a type of acute renal failure that rarely progresses to chronic renal impairment and long-term dialysis, has been reported for patients who took oral sodium phosphate. Renal tubular injury occurs from the deposition of calcium phosphate crystals in the distal tubules and collecting ducts, as shown histologically. Crystals form because of an abnormally high concentration of calcium phosphate from oral sodium phosphate–induced dehydration, decreased intravascular volume, and hyperphosphatemia, which is compounded further by reabsorption of water from renal tubules. Risk factors for acute phosphate nephropathy include advanced age (more severe in patients 57 years or older), decreased intravascular volume (eg, congestive heart failure, cirrhosis, or nephrotic syndrome), acute or chronic kidney disease, and concomitant use of drugs that affect renal perfusion or function (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and possibly nonsteroidal antiinflammatory drugs).

A saline laxative, milk of magnesia (15-30 mL once or twice daily), draws fluid osmotically into the lumen, stimulates the release of cholecystokinin, and accelerates colonic transit. It may cause hypermagnesemia, particularly in patients with renal insufficiency.

- Patients with slow-transit constipation can take saline laxatives or hyperosmolar agents daily and stimulant laxatives on an as-needed basis.
- Sorbitol is as effective but less expensive and less sweet than lactulose.
- Oral sodium phosphate solution should be used with care because rarely it causes acute phosphate nephropathy and renal failure.

Stimulant laxatives affect mucosal transport and motility. They include surface-active agents (docusate sodium [Colace], 100 mg orally twice daily), diphenylmethane derivatives, ricinoleic acid, anthraquinones, glycerin (suppository), and bisacodyl (10-mg tablet or suppository). Stool softeners such as docusate sodium are of limited efficacy. Glycerin and bisacodyl, taken up to once every other day, work by inducing colonic high-amplitude propagated contractions. Bisacodyl tablets take effect in 6 to 8 hours, and suppositories should be administered 30 minutes after eating to maximize synergism with the gastrocolic reflex. Of the diphenylmethane derivatives, phenolphthalein was withdrawn from the US market after animal studies suggested that it may be carcinogenic; however, no epidemiologic evidence supports this claim. The anthraquinone compounds may cause allergic reactions, electrolyte depletion, melanosis coli, and cathartic colon. *Melanosis coli* refers to brownish black colorectal pigmentation of unknown composition associated with apoptosis of colonic epithelial cells. *Cathartic colon* refers to altered colonic structure observed on barium enema studies and associated with long-term use of stimulant laxatives. The altered structure includes colonic dilatation, loss of haustral folds, strictures, colonic redundancy, and wide gaping of the ileocecal valve. Early reports implicating laxative-induced destruction of myenteric plexus neurons in cathartic colon have been disputed. Although anthraquinones may induce colorectal tumors in animal models, several cohort studies and a recent case-control study did not show an association between anthraquinones and colon cancer.

- Bisacodyl and glycerin facilitate defecation by inducing colonic high-amplitude propagated contractions.
- Melanosis coli indicates recent laxative use. The evidence linking anthraquinones to colon cancer and destruction of the myenteric plexus is inconclusive.

Both of the secretagogues (ie, lubiprostone and linaclotide) used to treat chronic constipation increase intestinal secretion of chloride, which is followed by the secretion of water into the lumen. Both drugs are approved by the US Food and Drug Administration for treating chronic constipation and constipation-predominant irritable bowel syndrome in adults. For these indications, linaclotide is approved for treating men and women, while lubiprostone is approved for women only. Lubiprostone is also approved for treating opioid-induced constipation in adult patients with chronic, noncancer pain. Lubiprostone is a bicyclic fatty acid derivative that promotes intestinal secretion by activating intestinal type 2 chloride channels. Lubiprostone accelerates colonic transit in healthy people but not in patients with chronic constipation. The effects of lubiprostone are more pronounced on stool consistency and frequency than on abdominal bloating, discomfort, and straining. Lubiprostone is well tolerated; nausea and headache are the most common adverse effects. In clinical trials, 33% of patients reported nausea, which generally was mild and could be reduced by taking the medication with meals.

- Lubiprostone stimulates intestinal secretion by activating chloride channels; it also improves stool consistency and relieves constipation.

Linaclotide is a first-in-class 14–amino acid peptide similar to the heat-stable enterotoxins (ST peptides) of *Escherichia coli* that cause traveler's diarrhea. It is a guanylate cyclase–C receptor agonist that increases the synthesis of cyclic guanosine monophosphate, which in turn induces signaling pathways that stimulate chloride and bicarbonate secretion through cystic fibrosis transmembrane regulator channel–dependent and, to a lesser extent, channel-independent mechanisms. Linaclotide also acts on a sodium proton exchanger to inhibit the absorption of sodium from the lumen. In contrast to lubiprostone, linaclotide accelerates colonic transit in constipation-predominant irritable bowel syndrome.

Newer serotoninergic 5-HT_4 agonists (eg, prucalopride) are more specific for 5-HT_4 receptors and have fewer cardiovascular effects than older 5-HT_4 agonists (eg, cisapride). They accelerate colonic transit in healthy people and, for some agonists, also in patients with chronic constipation. They also improve symptoms of chronic constipation. However, these agents are not approved for clinical use in the United States.

Emerging data suggest that bile acid transporter inhibitors may improve symptoms of chronic constipation. Normally, ileal

bile acid transporters (IBATs) absorb 97% of bile acids in the terminal ileum. Unabsorbed bile acids spill into the colon, where they are deconjugated and dehydroxylated by colonic microbiota to produce secondary bile acids, such as deoxycholic acid, which induce colonic secretion. The IBAT inhibitor A3309 has been found to accelerate colonic transit and improve bowel habits in patients with chronic constipation. In general, A3309 was well tolerated; abdominal cramps and diarrhea were the most common side effects. In a dose-dependent manner, A3309 also decreased total and low-density lipoprotein cholesterol levels, which may be particularly beneficial for older patients with chronic constipation. While promising, these results need to be confirmed with larger phase 3 trials.

Other pharmacologic approaches that have been used to manage slow-transit constipation include colchicine and misoprostol (Cytotec). Colchicine, 0.6 mg orally 3 times daily, and misoprostol, 1,200 mg daily, cause diarrhea. Colchicine should be used cautiously, if at all, for treating constipation, because long-term use may be associated with neuromyopathy. Other adverse effects include hypersensitivity reactions, bone marrow suppression, and renal damage. Misoprostol should not be used to treat constipation because it is expensive, may cause miscarriage in pregnant women, and may exacerbate abdominal bloating. Moreover, its beneficial effects appear to decrease with time.

- Colchicine and misoprostol are unproven, potentially deleterious agents for treating slow-transit constipation.

Enemas, including mineral oil retention enema, 100 to 250 mL daily per rectum; phosphate enema (Fleet), 1 unit per rectum; tap water enema, 500 mL per rectum; and soapsuds enema, 1,500 mL per rectum, are especially useful in patients with fecal impaction in the rectosigmoid colon, as may occur in obstructive defecation. All the preparations are contraindicated for patients with rectal inflammation, and phosphate enemas are contraindicated for patients with hyperphosphatemia or hypernatremia. Mineral oil taken orally is associated with lipid pneumonia, malabsorption of fat-soluble vitamins, dehydration, and fecal incontinence.

- Enemas may be used judiciously on an as-needed basis for constipation.

Surgical Therapy

Subtotal colectomy with ileorectal anastomosis is effective and occasionally indicated for patients with medically refractory, severe slow-transit constipation, provided that pelvic floor dysfunction has been excluded or treated. In patients with megarectum, the rectum is also resected. Postoperative ileus and delayed mechanical small-bowel obstruction each occur in approximately 10% of patients. Diarrhea is common shortly after the operation but tends to resolve with time. The importance of identifying and treating pelvic floor dysfunction with biofeedback therapy preoperatively in patients with slow-transit constipation cannot be overemphasized.

- Subtotal colectomy is necessary and beneficial for patients with slow-transit constipation that does not respond to medical management.

Disorders of Pelvic Floor Function

Disorders of pelvic floor function include functional defecatory disorders and fecal incontinence. Fecal incontinence, or involuntary leakage of stool from the anus, is a common symptom, particularly in the elderly. In community-based surveys, the prevalence of fecal incontinence among women 50 years or older approaches 15%. The prevalence among nursing home residents is as high as 40%. At Mayo Clinic, 50% of patients with chronic constipation had a component of pelvic floor dysfunction.

Physiology of Defecation

Rectal distention evokes the desire to defecate and induces relaxation of the internal anal sphincter by an involuntary reflex (Figure 20.3). Defecation is completed by adoption of a suitable posture, contraction of the diaphragm and abdominal muscles to increase intra-abdominal pressure, and relaxation of the puborectalis muscle and external anal sphincter, both striated muscles. Relaxation of the puborectalis muscle allows widening and lowering of the anorectal angle, with perineal descent (Figure 20.4).

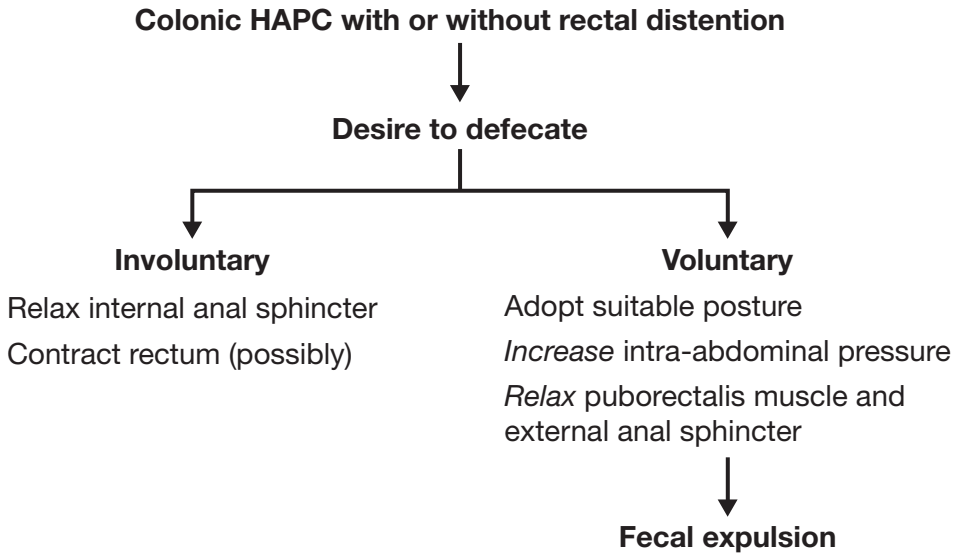

Figure 20.3. Physiology of Defecation. HAPC indicates high-amplitude propagated contraction. (Adapted from Bharucha AE, Camilleri M. Physiology of the colon. In: Zuidema GD, Yeo CJ, editors. Shackelford's surgery of the alimentary tract. Vol IV. 5th ed. Philadelphia [PA]: WB Saunders; c2002. p. 29-39. Used with permission.)

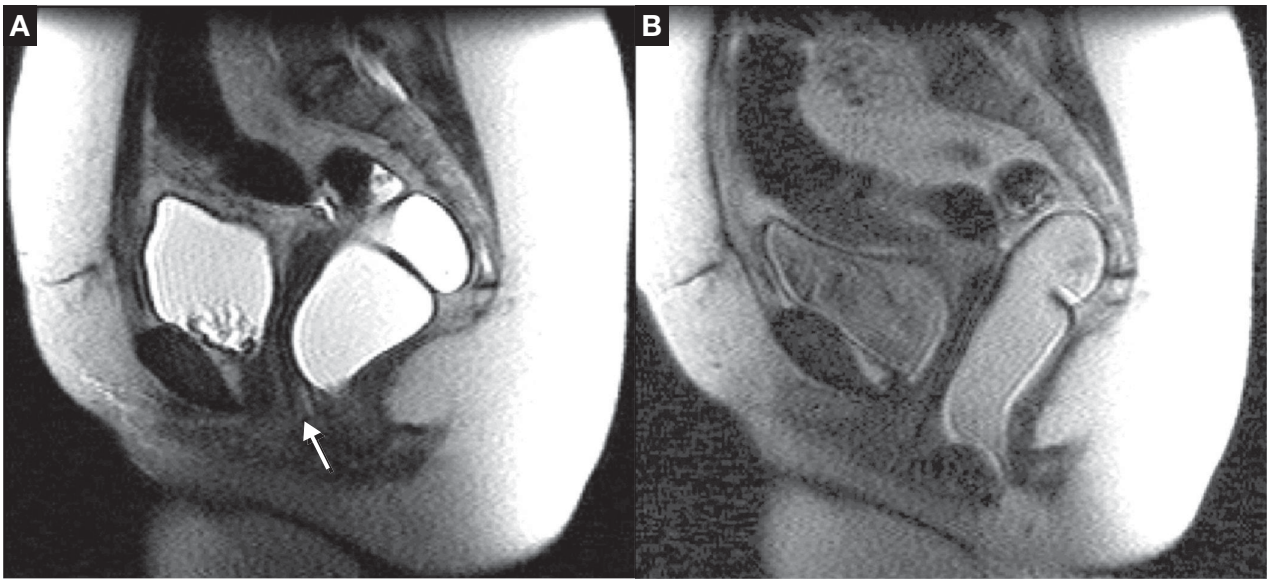

Figure 20.4. Magnetic Resonance Fluoroscopic Images of the Pelvis. A, At rest. B, During simulated defecation. Defecation is accompanied by opening of the anorectal junction (arrow), pelvic descent, and widening of the anorectal angle from 101° at rest to 124° during defecation. The rectum was filled with ultrasound gel.

The coordination between abdominal contraction and pelvic floor relaxation is crucial to the process. Although colonic high-amplitude propagated contractions may precede defecation, the contribution of rectal contraction to defecation is unclear.

Functional Defecatory Disorders

Functional defecatory disorders (also called *obstructive defecation, pelvic floor dyssynergia*, and *pelvic floor dysfunction*) are characterized by disordered defecation caused by functional obstruction that results from impaired relaxation of the external anal sphincter, impaired relaxation of the puborectalis muscle, or inadequate propulsive forces (ie, intrarectal pressure), or a combination of these. Although certain symptoms are considered suggestive of defecatory disorders (eg, frequent straining, a sensation of incomplete evacuation, dyschezia, and digital evacuation of feces), symptoms alone are not sufficiently specific for distinguishing between functional defecatory disorders and other causes of constipation (ie, normal-transit and slow-transit constipation). A thorough digital rectal examination with assessment of anal resting tone and anorectal motion when patients contract (ie, squeeze) and simulate evacuation is useful for identifying defecatory disorders. Anal resting pressure is gauged by the resistance to the insertion of a finger in the anal canal. When patients squeeze, the anal sphincter and puborectalis muscles contract; contraction of the puborectalis muscles lifts the palpating finger toward the umbilicus. Conversely, simulated evacuation should be accompanied by perineal descent (2-4 cm) and relaxation of the puborectalis muscle. In patients with functional defecatory disorders, digital rectal examination may show (alone or in combination) increased resting pressure or increased or decreased perineal descent. When rectal prolapse is suspected, patients should be examined in the seated position on a commode.

Tests

Anorectal tests are necessary because defecatory disorders cannot be identified by clinical features alone. Anorectal manometry and rectal balloon expulsion tests usually are sufficient to confirm or exclude functional defecatory disorders. In selected patients, defecography with barium or magnetic resonance imaging (MRI) may be necessary.

Anorectal Manometry. Anorectal manometry can be conducted with traditional (ie, water-perfused or solid-state) or high-resolution manometric catheters. The advantage of high-resolution manometric catheters is that sensors are evenly distributed along the catheter. Hence, when the catheter is positioned appropriately, the sensors straddle the entire anal canal, allowing pressures to be assessed without a pull-through maneuver, in contrast to traditional manometry.

Patients with defecatory disorder may have a high resting anal sphincter pressure or a reduced rectoanal pressure gradient (or both) during simulated defecation (Figure 20.5). Normal values for anal pressures measured with manometry vary by technique and are influenced by age, sex, and perhaps parity. Anal pressures are lower in women than in men and decrease with age, even in asymptomatic people. Contrary to current concepts, the utility of a low rectoanal pressure gradient in the diagnosis of defecatory disorders is unclear since values overlap considerably for this parameter among asymptomatic patients, patients with defecatory disorders, and patients with anorectal pain without constipation. Indeed, a majority of asymptomatic women have a negative rectoanal pressure gradient with high-resolution manometry. If a cautious approach is taken, a negative rectoanal gradient should not be used in isolation to diagnose defecatory disorders.

Rectal Balloon Expulsion Test. Rectal expulsion can be evaluated by asking patients to expel from the rectum balloons filled with water or air. One approach is to measure the time required to expel a rectal balloon while the patient is seated on a commode chair behind a privacy screen. Depending on the technique, patients with normal pelvic floor functions can expel a rectal balloon within 1 to 2 minutes. An alternative method is to measure, with the patient in the left lateral decubitus position, the traction required to expel a balloon connected over a pulley to a series of weights. Patients with pelvic floor dysfunction require more external traction to expel a balloon

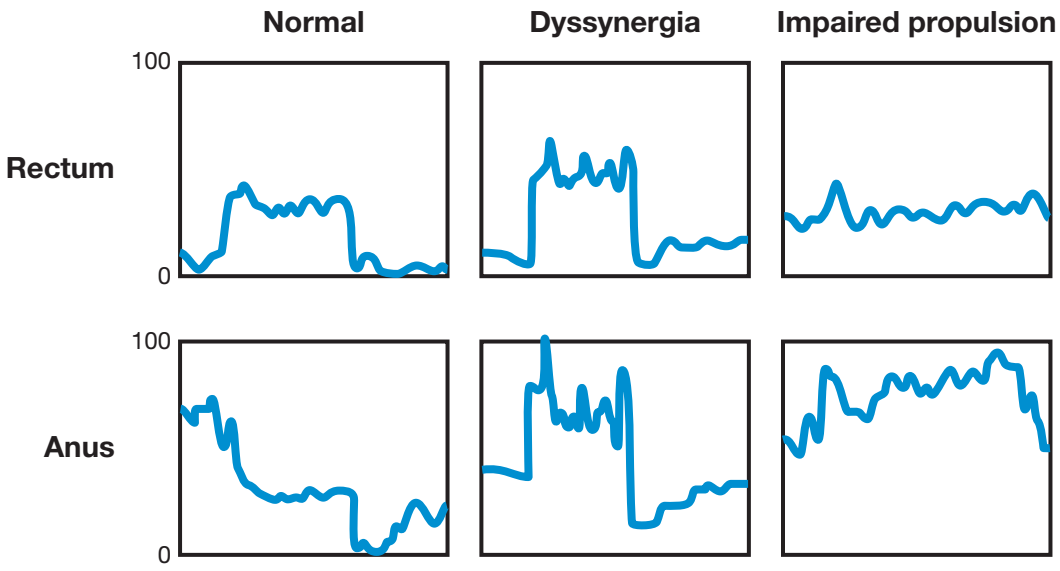

Figure 20.5. Rectoanal Pressure Profiles During Simulated Defecation. Left, In health, the normal pattern is increased rectal pressure and anal relaxation. Center and right, Patients with functional defecatory disorders (dyssynergia and impaired propulsion) may either paradoxically contract the anal sphincters (center) or generate inadequate rectal propulsive forces (right).

(Figure 20.6). The rectal balloon expulsion test is highly sensitive and specific (>85%) for identifying functional defecatory disorders. Moreover, an abnormal result on the rectal balloon expulsion test predicts the response to pelvic floor retraining by biofeedback therapy.

Barium or Magnetic Resonance Proctography. During dynamic (ie, barium or magnetic resonance [MR]) proctography, anorectal anatomy and pelvic floor motion are recorded with the patient resting, coughing, squeezing, and straining to expel barium from the rectum. The anorectal angle and position of the anorectal junction are tracked during these maneuvers, as are the retention and evacuation of contrast material. Dynamic imaging can identify inadequate or excessive perineal descent, internal rectal intussusception, rectoceles, sigmoidoceles, and enteroceles. Also, puborectalis muscle dysfunction can be characterized during squeeze and evacuation. MR proctography is preferred to barium proctography because 1) it does not entail radiation exposure, 2) it provides easier visualization of the bladder and uterus together with the anorectum, and 3) it provides more distinct visualization of the bony landmarks (pubis and sacrococcygeal junction) necessary to measure anorectal descent. Therefore, measurements of anorectal motion are more reproducible with MR proctography than with barium proctography. However, proctography findings need to be interpreted in the overall clinical context. For example, rectoceles are particularly common in multiparous subjects. Clinically important rectoceles are generally large (>3 cm) or fail to empty completely during defecation. Moreover, women with clinically important rectoceles often apply posterior vaginal pressure to facilitate defecation. Rectoceles usually are due to inadequate pelvic floor relaxation rather than to a primary abnormality.

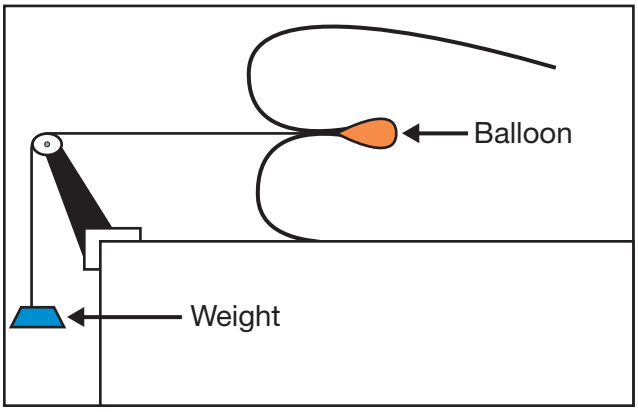

Figure 20.6. Balloon Expulsion Test. See text for details. (Adapted from Bharucha AE, Klingele CJ. Autonomic and somatic systems to the anorectum and pelvic floor. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Vol 1. 4th ed. Philadelphia [PA]: Elsevier Saunders; c2005. p. 279-98. Used with permission.)

Colonic Transit. Delayed colonic transit is common in defecatory disorders. Hence, the finding of slow colonic transit does not exclude the diagnosis of defecatory disorders.

- Anorectal manometry and the rectal balloon expulsion test generally are sufficient for diagnosing functional defecatory disorders; proctography is necessary in selected cases only.
- The rectal balloon expulsion test is highly sensitive and specific for diagnosing functional defecatory disorders, and an abnormal test result predicts the response to biofeedback therapy.
- Colonic transit is delayed in the majority of patients who have functional defecatory disorders.
- Because false-positive and false-negative results may occur, anorectal function tests need to be interpreted in the context of the clinical features. For example, in up to 20% of healthy controls, the anal sphincter paradoxically contracts instead of relaxes during evacuation.

Treatment

Pelvic floor retraining with biofeedback therapy improves symptoms in 70% of patients who have a functional defecatory disorder. Biofeedback therapy is conducted with sensors that measure surface electromyographic activity or pressures in the anorectum. By providing auditory or visual feedback of this activity,

patients are taught to relax the pelvic floor and improve coordination between the abdominal wall and diaphragmatic contraction and pelvic relaxation during defecation. Strong rapport between patients and therapists is critical for biofeedback therapy. Measures to contract the pelvic floor muscle (eg, Kegel exercises) are not appropriate for obstructive defecation. Controlled trials have shown that pelvic floor retraining is superior to laxatives for relieving constipation in patients with obstructive defecation. This symptomatic improvement has been sustained for 2 years. Biofeedback therapy also normalizes colonic transit and anal relaxation during defecation.

Fecal Incontinence

Fecal continence is maintained by anatomical factors and complex sensory and motor interactions among the sphincters, the anorectum, central and peripheral awareness, and the physical ability to get to a toilet. *Fecal incontinence* is defined as the involuntary leakage of liquid or solid stool from the anus; anal incontinence also includes leakage of gas. Up to 40% of nursing home residents have fecal incontinence, which is also common in the community. Up to 10% of all women and 20% of women 40 years or older in the community have fecal incontinence. Patients with chronic fecal incontinence lead a restricted lifestyle, are afraid of having an embarrassing episode, and often miss work. The symptom frequently coexists with urinary incontinence and contributes to institutionalization. People with fecal incontinence are embarrassed to admit to their family and physician that they have this condition, even though their symptoms may affect their quality of life significantly. Therefore, it is essential to ask patients with diarrhea or diabetes mellitus whether they have incontinence.

Etiology

In most patients, fecal incontinence is attributable to disordered anorectal continence mechanisms compounded by bowel disturbances, generally diarrhea. Several important diseases, summarized below, contribute to fecal incontinence.

Sphincter Damage. Sphincter damage includes obstetric and surgical (eg, hemorrhoidectomy) damage. Known obstetric risk factors for sphincter damage include forceps delivery, median episiotomy, and high birth weight.

Pudendal Neuropathy. Pudendal neuropathy may be attributable to obstetric trauma or diabetes mellitus. Also, patients with constipation may strain excessively during defecation and cause stretch injury to the pudendal nerve, soft tissue laxity, and excessive perineal descent. Eventually, sphincter weakness develops, predisposing to fecal incontinence.

Neurologic Causes. Neurologic causes include multiple sclerosis, Parkinson disease, Alzheimer disease, stroke, diabetic neuropathy, and cauda equina or conus medullaris lesions. Cauda equina lesions that cause fecal incontinence usually are accompanied by other neurologic symptoms and signs.

Other Local Causes. Examples of other local causes are perianal sepsis, radiation proctitis, and systemic sclerosis. In radiation proctitis, the entry of stool into a noncompliant (stiff) rectum may overwhelm continence mechanisms and cause incontinence. Scleroderma is associated with fibrosis of the internal anal sphincter and weak resting pressures.

Diarrhea. Fecal incontinence is a common complication of irritable bowel syndrome, cholecystectomy, and inflammatory bowel disease.

Assessment

Patients with diarrhea must be asked specifically about fecal incontinence because they may not volunteer the information. The severity, risk factors, and circumstances of fecal incontinence and its effect on lifestyle should be assessed. Patients with *urge incontinence* generally are incontinent only for liquid or semiformed stools, have a brief warning, and are unable to reach the toilet in time. In contrast, patients with *passive incontinence* are aware of stool leakage only after the episode. Patients with urge incontinence have decreased anal squeeze pressure or squeeze duration (or both), whereas those with passive incontinence have reduced anal resting pressure. Some patients with urge fecal incontinence also may have rectal hypersensitivity, perhaps from a stiffer rectum. Nocturnal fecal incontinence occurs in patients with diabetes mellitus or scleroderma and is suggestive of weakness of the internal anal sphincter. A complete physical examination should include perianal assessment to identify common causes of perianal soiling, such as hemorrhoidal prolapse, perianal fistula, rectal mucosal prolapse, fecal impaction, anal stricture, and rectal mass. The perianal area must be inspected closely with the patient in the left lateral decubitus position and with the patient seated on the toilet. A thorough digital examination, as described above, should be performed. Flexible sigmoidoscopy, with or without anoscopy, is the final component in this phase of evaluation.

Tests

A combination of tests is necessary to evaluate the various components of anorectal anatomy and function. For each patient, the intensity of investigation depends on the patient's age, severity of fecal incontinence, clinical assessment of risk factors and anal sphincter pressures, and response to previous therapy (Figure 20.7).

Anorectal Manometry. Frequently, anal resting and squeeze pressures are decreased in fecal incontinence. Anal pressures should be compared with normal values obtained with the same technique in age- and sex-matched asymptomatic people. Among patients with weak or normal anal pressures, other factors (eg, diarrhea or disturbances of rectal compliance or sensation) also may contribute to fecal incontinence.

Anal Ultrasonography. Anal ultrasonography reliably identifies anatomical defects or thinning of the internal anal sphincter and defects of the external anal sphincter that often are unrecognized clinically or are amenable to surgical repair (or both). However, compared with the interpretation of images of the internal sphincter, the interpretation of images of the external anal sphincter is more subjective, operator dependent, and confounded by normal anatomical variations of the external anal sphincter. Results of prospective studies have suggested that an external anal sphincter defect develops in up to one-third of women after a vaginal delivery. Therefore, it can be challenging to interpret the clinical significance of anal sphincter defects—that is, the extent to which a sphincter defect explains anal weakness.

Evacuation Proctography. Dynamic proctography is indicated for fecal incontinence when clinical features suggest excessive perineal descent, a significant rectocele (eg, in patients who

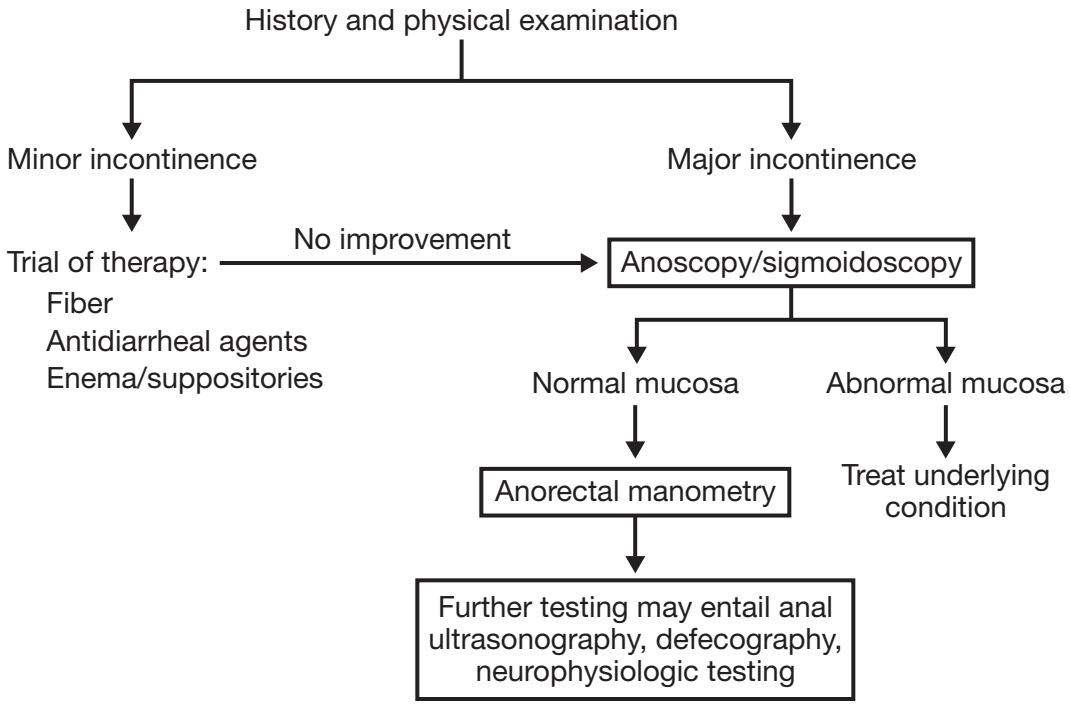

Figure 20.7. **Algorithmic Approach to Fecal Incontinence.**

splint the vagina to facilitate rectal emptying), an enterocele, or internal rectal intussusception.

Sphincter Denervation Measurements. The pudendal nerve may be injured (with or without damaging the sphincter) during vaginal delivery or by repetitive straining in patients with chronic constipation. Pudendal nerve terminal motor latency (PNTML) can be measured by placing the examining finger, covered by a glove containing stimulating and recording electrodes, as close as possible to the pudendal nerve as it courses around the pelvic brim. PNTML measures the function of the fastest conducting fibers. Initial studies showed prolonged PNTML in fecal incontinence. However, PNTML measurements are operator dependent and lack adequate sensitivity and specificity for identifying pudendal nerve damage. Patients with prolonged PNTML may have normal anal canal squeeze pressures. In contrast to earlier studies, recent data have suggested that prolonged PNTML does not predict success after surgical repair of sphincter defects. According to a position statement from the American Gastroenterological Association, PNTML should not be used to evaluate fecal incontinence. Needle electromyographic examination of the external anal sphincter provides a sensitive measure of denervation and usually can identify myopathic, neurogenic, or mixed injury.

Rectal Compliance and Sensation. Sensation is assessed by asking patients to report when they perceive the first detectable sensation, the desire (or urgency) to defecate, and maximal tolerable discomfort during rectal balloon distention, generally with a handheld syringe. Alternatively, a balloon can be inflated at a controlled rate with a barostat, which is a continuous-infusion pump. During distention with a barostat, rectal pressures and volumes and, thus, rectal compliance (pressure-volume relationships) and capacity also can be assessed. Rectal sensation may be normal, decreased, or increased in fecal incontinence. When rectal sensation is decreased, stool may leak before the external anal sphincter contracts. By improving rectal sensation, sensory retraining can restore the coordinated contraction of the external anal sphincter and improve fecal continence. Conversely, other patients with fecal incontinence have exaggerated rectal sensation, perhaps because of a stiffer or smaller rectum.

Pelvic MRI. MRI is a relatively new method for imaging anal sphincter anatomy and pelvic floor motion during defecation and squeeze without radiation exposure. The anal sphincters also can be visualized, preferably with an endoanal MRI coil. MRI is superior to ultrasonography for visualizing morphologic features, particularly atrophy, of the external anal sphincter. In contrast to evacuation proctography, dynamic MRI does not entail radiation exposure and it directly visualizes the pelvic floor, including the anterior (bladder) and middle (uterus) compartments.

Treatment

Much can be accomplished by regulating bowel habits in patients with diarrhea or constipation. Diarrhea should be managed by treatment of the underlying condition (eg, antibiotics for small intestinal bacterial overgrowth and dietary restriction for carbohydrate malabsorption) or with antidiarrheal agents, which must be prescribed in adequate doses. Loperamide hydrochloride (2 mg; maximal dose, 16 mg daily), diphenoxylate hydrochloride with atropine sulfate (5 mg), or codeine sulfate (30-60 mg) may need to be taken regularly, preferably 30 minutes before meals, perhaps up to several times daily. Loperamide not only delays gastrointestinal transit but also improves anal resting tone. Similarly, amitryptyline improves fecal continence by restoring stool consistency and reducing rectal irritability. The bile-acid binding resins cholestyramine and colesevelam are useful for patients with postcholecystectomy diarrhea. Scheduled rectal emptying with suppositories or enemas is often useful for fecal impaction and overflow incontinence.

The results of uncontrolled studies have suggested that biofeedback therapy improves symptoms in up to 70% of patients with fecal incontinence, particularly those with partially preserved rectal sensation. In a controlled trial, 171 patients with fecal incontinence were assigned randomly to 4 groups: standard medical and nursing care (advice only), advice and verbal instruction on sphincter exercises, hospital-based computer-assisted sphincter pressure biofeedback, and hospital biofeedback and use of a home electromyographic biofeedback device. Overall, 55% of patients reported improved symptoms and 5% were cured. Improvement was sustained at 1 year after therapy, and symptoms and resting and squeeze pressures improved to a similar degree in all 4 groups. These results underscore the importance that patients attach to understanding the condition, to practical advice about coping strategies (eg, diet and skin care), and to nurse-patient interaction. However, the usefulness of biofeedback therapy over and above that of other conservative measures was unclear.

This question was assessed by another controlled trial of 108 patients, in which 22% had a response to 4 weeks of conservative therapy. Among the other 65 patients who did not respond and continued with the study, the response rates were better for those who received 6 biweekly sessions with electromyographically assisted biofeedback and pelvic floor exercises (77% reported adequate relief and 66% were completely continent) than for those who had pelvic floor exercises alone (41% reported adequate relief and 48% were completely continent). These preliminary data support the use of biofeedback therapy for patients with fecal incontinence that does not respond to other conservative measures. Poor prognostic factors include total absence of rectal sensation, dementia, sphincter denervation, and megarectum. Success is highly dependent on the motivation of the patient and the rapport between the patient and therapist.

Continence improves in 80% to 90% of patients shortly after repair of anal sphincter defects but deteriorates over time thereafter; less than 20% of patients are continent at 5 years after the operation. Several predominantly uncontrolled studies have suggested that sacral nerve stimulation may improve fecal continence. Sacral nerve stimulation is now approved for treating urinary and fecal incontinence. Artificial anal sphincter and dynamic graciloplasty are associated with considerable morbidity, particularly wound infections, and are used sparingly in the United States. A colostomy is often the last resort for patients with medically refractory fecal incontinence.

- Conservative measures, including management of bowel disturbances, often improve fecal continence.
- Patients who do not benefit from conservative measures alone may benefit from pelvic floor retraining.
- Fecal continence improves in the short term but deteriorates over time after surgical repair of anal sphincter defects.

Suggested Reading

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21

Gastrointestinal Disease and Pregnancy[a]

SUNANDA V. KANE, MD

Pharmacotherapy for the management of common gastrointestinal illnesses has evolved remarkably since the late 1990s. Women with chronic illnesses who would have been unwilling or unable to conceive in the past are now healthy enough to consider pregnancy. In addition, many women are deferring childbearing until later in life, when polypharmacy and illness may be more common. This chapter discusses the use of medications during pregnancy according to the best available evidence. Because the amount of high-quality controlled data in pregnancy is limited, absolute safety is not guaranteed with any medication. Instead, the risk of the underlying condition and the safety of the medications used to treat it should be balanced against the overall health of the mother and the fetus in each case. All conversations about medications, along with possible consequences of not treating the disease during pregnancy, should be documented carefully. Communication with the patient's obstetrician during this time is also paramount.

This chapter covers the treatment of common gastrointestinal and liver diseases, the management of common gastrointestinal symptoms, and the use of medications during endoscopy. The majority of medications can be categorized on the basis of existing reports; the categories are summarized in Table 21.1.

Endoscopy

Endoscopy constitutes a large portion of the gastroenterologist's role in patient care. Although many pregnant women have appropriate indications for endoscopy, fetal drug safety is a major consideration in the choice and dosage of endoscopic medications. For particularly high-risk endoscopy, such as therapeutic endoscopic retrograde cholangiopancreatography (ERCP), an anesthesiologist may be helpful in titration of medications and patient monitoring. For patients who present with gastrointestinal tract hemorrhage, in which diagnosis and therapeutic intervention are necessary, therapeutic scopes should be used. The use of medications for endoscopy is summarized in Table 21.2.

Meperidine

Meperidine is transferred rapidly across the placenta. Physicians have extensive experience prescribing meperidine during pregnancy, particularly during labor. Two large studies did not show teratogenicity from the administration of meperidine during the first trimester. The Collaborative Perinatal Project, a national study with the primary aim of documenting the teratogenicity of drugs taken during the first 4 months of pregnancy, followed more than 50,000 women in 12 US centers between 1959 and 1965 and reported no teratogenicity from meperidine use in 268 mothers with first-trimester exposure. Meperidine is preferred to morphine for obstetric pain because it is slower to cross the fetal blood-brain

[a] Portions of this chapter were adapted from Mahadevan U, Kane S. American Gastroenterological Association Institute technical review on the use of gastrointestinal medications in pregnancy. Gastroenterology. 2006 Jul;131(1):283-311; Mahadevan U. Gastrointestinal medications in pregnancy. Best Pract Res Clin Gastroenterol. 2007;21(5):849-77; and Mahadevan U, Kane S. American Gastroenterological Association Institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology. 2006 Jul;131(1):278-82. Used with permission.

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; FDA, US Food and Drug Administration; H_2, histamine$_2$; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; TREAT, Crohn's Therapy, Resource, Evaluation, and Assessment Tool; UDCA, ursodeoxycholic acid

Table 21.1. US Food and Drug Administration (FDA) Categories for the Use of Medications in Pregnancy

FDA Category	*Definition*
A	Controlled studies in animals and women have shown no risk in the first trimester, and possible fetal harm is remote
B	Either animal studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester
C	No controlled studies in humans have been performed, and animal studies have shown adverse events, or studies in humans and animals are not available; give the medication if the potential benefit outweighs the risk
D	Positive evidence of fetal risk is available, but the benefits may outweigh the risk if the disease is life-threatening or serious
X	Studies in animals or humans show fetal abnormalities; the drug is contraindicated

barrier. Meperidine can cause diminished fetal beat-to-beat cardiac variability that lasts for approximately 1 hour after being administered intravenously to the mother and is a common cause of decreased fetal cardiac variability during endoscopy.

The labeling approved by the US Food and Drug Administration (FDA) for meperidine carries the following warning: "Meperidine should not be used in pregnant women prior to the labor period, unless in the judgment of the physician the potential benefits outweigh the possible risks, because safe use in pregnancy prior to labor has not been established relative to possible effects on fetal development." Meperidine is preferred to diazepam or midazolam as an endoscopic premedication during pregnancy. The meperidine dosage should be titrated to produce calmness, restfulness, and mild analgesia without somnolence.

Fentanyl

Fentanyl is rated a category C drug during pregnancy, and accumulated anecdotal experience suggests that it may be used in low doses for endoscopy. Fentanyl is sometimes used as an alternative to meperidine during endoscopy because of its more rapid onset of action. In several human studies, administration of fentanyl to the mother during labor produced no neonatal toxicity.

Propofol

Propofol is a category B drug and is now a preferred agent for sedation in some endoscopy centers. However, it has not been studied extensively in women in the first and second trimesters and, thus, is not recommended for use during this time, based on the dearth of studies in the obstetric literature. Propofol rapidly transfers across the placenta near term. In 1 study, 20 infants exposed to propofol during parturition had depressed Apgar scores at birth compared with unexposed controls, but the neurodepression rapidly reversed. Numerous other studies have not demonstrated any neonatal toxicity when propofol was administered during parturition; however, the safety of exposure in the first trimester has not been studied adequately.

Naloxone

The FDA classifies naloxone as a category B drug during pregnancy. In opiate-dependent patients, small doses of naloxone precipitate a syndrome resembling that produced by opiate withdrawal. Symptoms include restlessness, anxiety, insomnia, irritability, hyperalgesia, nausea, and muscle cramps. Because opiates cross the placenta, the administration of naloxone is dangerous and contraindicated in a pregnant patient who is specifically opiate dependent. The FDA-approved labeling for naloxone has the following precaution about use during pregnancy: "Naloxone should be used in pregnancy only if clearly needed." The administration of naloxone is appropriate, however, for pregnant patients who have serious signs of potential meperidine toxicity, such as respiratory depression, systemic hypotension, or unresponsiveness.

Table 21.2. Medications Used for Endoscopy

Drug	*FDA Category*	*Recommendations for Pregnancy*	*Recommendations for Breastfeeding*
Ampicillin	B	Safe to use when required	Compatible
Benzocaine	C	Avoid unless benefit outweighs risk	No human data: potential toxicity
Diatrizoate	D	Minimal use for therapeutic ERCP	Limited human data: probably compatible
Diazepam	D	Midazolam is the preferred benzodiazepine	Limited human data: potential toxicity
Electricity	None	Use for therapeutic ERCP	No human data: potential toxicity
Epinephrine	C	Avoid unless for hemostasis	No human data: potential toxicity
Fentanyl	C	Use in low doses	Compatible
Flumazenil	C	Only for severe benzodiazepine overdose	No human data: probably compatible
Glucagon	B	Avoid except for ERCP	No human data
Lidocaine	B	Gargle and spit (oral form)	Limited human data: probably compatible
Meperidine	B	Use in low doses	Compatible
Midazolam	D	Use in low doses	Limited human data: potential toxicity
Naloxone	B	Only for severe narcotic overdoses	No human data: probably compatible
Piperacillin-tazobactam	B	Useful in cholangitis or biliary sepsis	Safe
Polyethylene glycol electrolyte	C	No human studies available	Probably safe
Propofol	B	Avoid in first and second trimesters	Limited human data: probably compatible
Simethicone	C	Can be avoided but low risk	No human data: probably compatible
Sodium glycol electrolyte	C	Low risk with 1-time use	No human data

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; FDA, US Food and Drug Administration.

Benzodiazepines

Diazepam and midazolam, category D drugs, should have restricted use during endoscopy, particularly during the first trimester. Benzodiazepines, including diazepam and midazolam, are commonly administered before gastrointestinal endoscopy to reduce anxiety, induce brief amnesia, and produce muscle relaxation. Diazepam freely and rapidly crosses the placenta and accumulates in the fetal circulation at levels equal to or higher than those of maternal serum. The FDA-approved labeling for diazepam carries the following warning about use in pregnancy: "An increased risk of congenital malformations associated with the use of minor tranquilizers . . . during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided." Diazepam is not recommended by the American Academy of Pediatrics because it, along with its metabolite *N*-demethyldiazepam, can accumulate in breastfed infants.

Many endoscopists prefer midazolam to diazepam for endoscopic premedication because of faster onset and recovery time, more intense transient antegrade amnesia, and lower risk of thrombophlebitis. Midazolam crosses the human placenta, but fetal serum levels increase to only about one-third to two-thirds of those of maternal serum after oral, intramuscular, or intravenous administration in the mother. Midazolam appears to be preferable to diazepam for endoscopy during pregnancy because of the potential association between diazepam and oral clefts and neonatal neurobehavioral abnormalities. Because the mechanism of action is similar to that of diazepam, midazolam should be used cautiously and in low doses during pregnancy, particularly during the first trimester. Dosages should be titrated carefully to an end point of relaxation and calmness but not somnolence.

Flumazenil

Flumazenil, a category C drug, is a benzodiazepine antagonist that rapidly reverses the central effects of benzodiazepines. Little is known about the safety of flumazenil during pregnancy or in infants; thus, it should be used during pregnancy only if the potential benefit clearly outweighs the risks. The need for flumazenil can be prevented by carefully and slowly titrating the benzodiazepine dosage and by using the minimal benzodiazepine dosage required for endoscopic examination.

Simethicone

The FDA has classified simethicone as a category C drug. Many endoscopists use simethicone to reduce gastric foam before upper endoscopy. A surveillance study of Michigan Medicaid patients did not show a statistically significant difference between pregnant women exposed to the drug and those not exposed to it. Simethicone use is low risk during endoscopy because it is not absorbed systemically.

Glucagon

The FDA classifies glucagon as a category B drug during pregnancy. However, no adequate and well-controlled studies have involved pregnant women. Thus, this drug should be used during pregnancy only if clearly needed. Although fetal risk has not been characterized completely, the administration of glucagon appears to be justified to decrease intestinal motility to help reduce procedure time and to aid in cannulation of the bile duct and sphincterotomy during therapeutic ERCP, which is performed because of the high risk of untreated maternal cholangitis. If electrocautery is used, the grounding pad should be positioned so that the uterus is not directly between the electrical catheter and the grounding pad.

Antibiotics

Ampicillin

The FDA classifies ampicillin as a category B drug during pregnancy. This penicillin antibiotic may be used when *Enterococcus* infection is a concern. Ampicillin rapidly crosses the placenta, and fetal serum levels equilibrate with those of the maternal serum within 3 hours after the drug is administered to the mother.

Piperacillin-Tazobactam

Piperacillin-tazobactam, in FDA category B, is a good choice for pregnant patients who present with features of cholangitis or biliary sepsis. It may also be used before ERCP as prophylaxis against biliary sepsis when an obstructed biliary tree is suspected. Piperacillin-tazobactam covers most biliary and enteric pathogens (eg, *Escherichia* and *Klebsiella*) and also covers *Enterococcus* species. The drug does cross the placenta but is deemed safe in all trimeters of pregnancy. This antibiotic may also be used in women who breastfeed.

Colonic Lavage Preparations

Polyethylene glycol electrolyte solution has not been studied extensively in pregnancy, and it is not known whether it can cause fetal harm. A study of 225 patients showed that the agent was safe when used to treat constipation. Because full colonoscopy rarely is indicated during pregnancy, tap water enemas are recommended as bowel preparation for lower endoscopy.

Topical Anesthetics

Lidocaine

Lidocaine, an FDA category B drug, can be applied topically to the oropharynx before upper endoscopy and ERCP, although it is rarely needed. Additionally, lidocaine gel can be used topically around the perianal area before lower endoscopy in patients with painful hemorrhoids and fissures. No fetal harm was noted during parturition in the Collaborative Perinatal Project, in which 293 infants were exposed in the first trimester. The pregnant patient who is administered topical lidocaine should be instructed to gargle and spit out the preparation, rather than swallow it, to minimize systemic absorption.

Benzocaine

Benzocaine aerosols, gels, and solutions are used to anesthetize the oropharynx before upper endoscopic procedures. However, benzocaine is an FDA category C drug and should be considered only if the benefit of the medication outweighs the risk to the fetus.

Therapeutic Agents for Hemostasis

Epinephrine is injected during endoscopy to achieve hemostasis of actively bleeding lesions. During therapeutic endoscopy,

epinephrine is used to stop active bleeding; in this clinical scenario, the benefit outweighs the potential risk of its use.

Electricity is transferred readily across the uterus because amniotic fluid is an excellent conductor. Fetal risk depends on the voltage and on the current amplitude, duration, and frequency as well as on the location on the body. Fetal mortality is rare from electroconvulsive therapy or direct current cardioversion during pregnancy. During endoscopy, bipolar electrocautery should be used because no grounding pad is necessary.

Contrast Dye

Diatrizoate, a contrast agent injected into the biliary tree, has been used in diagnostic and therapeutic amniography without harming the fetus. Although it has been documented to impair fetal thyroid function and is an FDA category D medication, the risk of its use for cholangiography is less than for amniography because of the doses used. In the appropriate clinical setting, the risk of maternal cholangitis likely outweighs the theoretical risk of transient fetal hypothyroidism.

Nausea and Vomiting

Nausea and vomiting are extremely common during pregnancy and have multiple causes. Most women can be supported through episodes without the use of antiemetics. However, for women who have a protracted course or underlying conditions that may predispose to nausea and vomiting, medical therapy is warranted to prevent complications from volume depletion. The use of antiemetic medications during pregnancy is summarized in Table 21.3.

Pyridoxine

The first-line therapy for nausea and vomiting during pregnancy is pyridoxine (vitamin B_6). Several randomized controlled trials have demonstrated its effectiveness at 10 to 25 mg every 8 hours in the treatment of nausea and vomiting during pregnancy. Pyridoxine in combination with doxylamine has also been shown to be effective and safe and is classified in FDA category A.

Metoclopramide

The use of metoclopramide as an antiemetic usually is confined to the first trimester, but it also is used to enhance gastric emptying throughout pregnancy. A Danish study compared, over a 5-year period, 309 women who had singleton pregnancies and prescriptions for metoclopramide with 13,327 controls. The study reported no major differences in the risk of malformations (odds ratio [OR], 1.11; 95% CI, 0.6-2.1); low birth weight (OR, 1.79; 95% CI, 0.8-3.9); or preterm delivery (OR, 1.02; 95% CI, 0.6-1.7). While metoclopramide is an FDA category B medication, the risk of metoclopramide-induced movement disorders with long-term use needs to be considered.

Prochlorperazine

Prochlorperazine, a category C drug, readily crosses the placenta. However, most studies have not found an increased risk of adverse outcomes in pregnancy.

Promethazine

Promethazine is another category C drug. It is an antihistamine that is used occasionally as an antiemetic during pregnancy and also as adjunctive therapy for narcotics during labor.

Trimethobenzamide

Trimethobenzamide is a category C drug. Three studies have followed outcomes among women who took trimethobenzamide during the first trimester for nausea and vomiting. In all 3 studies, there was no increase in the incidence of malformations with the use of trimethobenzamide.

Ondansetron

Ondansetron, a category B drug, is used for the prevention and treatment of chemotherapy-induced nausea and vomiting and for hyperemesis gravidarum. A randomized, double-blind study compared intravenous ondansetron with promethazine for hyperemesis. Ondansetron was well tolerated and efficacious with no adverse effects; however, outcomes among infants were not reported. Results from teratogen information services databases do not show an increase in major malformations in comparison with exposure to other antiemetics or healthy controls.

Granisetron and Dolasetron

Both granisetron and dolasetron are category B drugs. There have not been any studies on pregnant women exposed to these agents. However, studies of pregnant rats and rabbits that were given up to 146 times the human dose did not show any adverse outcomes.

Domperidone

Domperidone, a category C drug, is a dopamine antagonist used for short-term treatment of nausea and vomiting and for its

Table 21.3. Medications Used for Nausea and Vomiting During Pregnancy

Drug	*FDA Category*	*Recommendations for Pregnancy*	*Recommendations for Breastfeeding*
Dolasetron	B	No human studies	No human data: probably compatible
Domperidone	C	Safety unknown	Limited human data: probably compatible
Granisetron	B	No human studies	No human data: probably compatible
Metoclopramide	B	No teratogenicity; low risk (population-based study)	Limited human data: potential toxicity
Ondansetron	B	No teratogenicity; low risk (controlled trial)	No human data: probably compatible
Prochlorperazine	C	No teratogenicity; low risk (large database study)	No human data: potential toxicity
Promethazine	C	No teratogenicity; low risk (large database study)	No human data: probably compatible
Pyridoxine	A	Considered safest therapy for nausea and vomiting; available without prescription	Compatible
Trimethobenzamide	C	No teratogenicity; low risk (case series)	No human data: probably compatible

Abbreviation: FDA, US Food and Drug Administration.

prokinetic properties. Currently, it is not available in the United States by prescription. Whether it crosses the placenta is not known, but its bioavailability after oral ingestion is low.

Gastroesophageal Reflux Disease

Heartburn is estimated to occur in 30% to 50% of pregnancies. For mild symptoms, only lifestyle and dietary modifications may be required. Medications for treating gastroesophageal reflux disease have not been tested routinely in randomized controlled trials with pregnant women. The medications used to treat gastroesophageal reflux disease and peptic ulcer disease are summarized in Table 21.4.

Antacids

Antacids that contain magnesium, aluminum, or calcium are not teratogenic in animal studies. Although 1 case-control study reported a significant increase in major and minor congenital abnormalities in infants exposed to antacids during the first trimester of pregnancy, no analysis of individual agents was done and, currently, most antacids at normal therapeutic doses are considered acceptable during pregnancy. Magnesium trisilicate, found in alginic acid, can lead to fetal nephrolithiasis, hypotonia, and respiratory distress if used long term and in high doses. Antacids containing sodium bicarbonate should not be used because they can cause maternal or fetal metabolic alkalosis and fluid overload. Excessive intake of calcium carbonate can result in milk-alkali syndrome, characterized by hypercalcemia, renal impairment, and metabolic alkalosis. None of the antacids have been shown to concentrate in breast milk and are acceptable when breastfeeding.

Sucralfate

Sucralfate, a category B drug, is a nonabsorbable drug that exerts a local rather than systemic effect and has been tested in a prospective randomized controlled trial. Women with gastroesophageal reflux disease treated with sucralfate had a higher frequency of symptomatic remission than controls (90% vs 43%, $P<.05$).

Cimetidine

Cimetidine is a category B drug. Multiple large cohort studies have shown that the rate of major birth defects among pregnant women taking cimetidine is the same as that for healthy controls.

Ranitidine

Ranitidine, like the other histamine$_2$ (H_2) blockers, is a category B drug. In the most recently published study of ranitidine use during pregnancy, data were collected prospectively from a large network database for teratology information. The study reported on 335 pregnant women exposed to ranitidine, 113 to cimetidine, 75 to famotidine, and 15 to nizatidine. The incidence of premature deliveries was higher in the exposed group than in the control group, but there was no increase in the incidence of major malformations. The authors concluded that there was no indication of an increased risk of major malformations after the use of H_2 blockers during pregnancy.

Famotidine and Nizatidine

Although both famotidine and nizatidine are category B drugs, the relatively smaller amount of data available from animal

Table 21.4. Medications Used for Gastroesophageal Reflux and Peptic Ulcer Disease

Drug	*FDA Category*	*Recommendations for Pregnancy*	*Recommendations for Breastfeeding*
		Antacids	
Aluminum-containing antacids	None	Most safe: minimal absorption	Low risk
Calcium-containing antacids	None	Most safe: minimal absorption	Low risk
Magnesium-containing antacids	None	Most safe: minimal absorption	Low risk
Magnesium trisilicates	None	Avoid long-term use or high doses	Low risk
Sodium bicarbonate	None	Not safe: alkalosis	Low risk
		Mucosal Protectants	
Sucralfate	B	Safe	No human data: probably compatible
		Histamine$_2$ Receptor Antagonists	
Cimetidine	B	Controlled data: low risk	Compatible
Famotidine	B	Paucity of safety data	Limited human data: probably compatible
Nizatidine	B	Limited human data (low risk in animals)	Limited human data: probably compatible
Ranitidine	B	Low risk	Limited human data: probably compatible
		Proton Pump Inhibitors	
Dexlansoprazole	B	Limited data: low risk	No human data: potential toxicity
Esomeprazole	B	Limited data: low risk	No human data: potential toxicity
Lansoprazole	B	Limited data: low risk	No human data: potential toxicity
Omeprazole	C	Embryonic and fetal toxicity	Limited human data: potential toxicity
Pantoprazole	B	Limited data: low risk	No human data: potential toxicity
Rabeprazole	B	Limited data: low risk	No human data: potential toxicity
		Promotility Agents	
Cisapride	C	Controlled study: low risk, limited availability	Limited human data: probably compatible
Metoclopromide	B	Low risk	Limited human data: potential toxicity
		Treatment of *Helicobacter pylori* Infection	
Amoxicillin	B	Safe	Compatible
Bismuth	C	Not safe: teratogenicity	No human data: potential toxicity
Clarithromycin	C	Avoid in first trimester	No human data: probably compatible
Metronidazole	B	Low risk; avoid in first trimester	Limited human data: potential toxicity
Tetracycline	D	Not safe: teratogenicity	Compatible

Abbreviation: FDA, US Food and Drug Administration.

and human studies compared with that for other H_2 blockers makes the choice of another agent prudent. Studies of animals treated with nizatidine, at 300 times the recommended human dose, reported more abortions, lower fetal weight, and fewer live fetuses among the treated animals than among the controls. Another study showed a higher rate of abortions in rabbits treated with large doses of the drug.

Promotility Agents

Metoclopramide

Metoclopramide is a category B drug. No congenital malformations or other neonatal toxicities have been reported in humans with the use of metoclopramide. Reproductive studies in mice, rats, and rabbits that received up to 250 times the recommended human dose have not demonstrated any increase in fetal toxicity. Metoclopramide has been used as a lactation stimulant, and the total daily dose that would be consumed by a nursing infant if the mother took 30 mg daily is much less than the maximum daily dose of 500 mcg/kg recommended for infants. Therefore, maternal doses of 45 mg or less daily should not have adverse effects on a breastfeeding infant.

Cisapride

Cisapride is a category C drug. A prospective, multicenter study compared the outcomes of 129 Canadian women who took cisapride between November 1996 and November 1998 with those of matched controls. No differences in the rates of major or minor congenital malformations were reported for the 2 groups. In July 2000, Janssen Pharmaceutica removed cisapride from the market because of concern about cardiovascular effects, and it is available only through a limited-access program.

Omeprazole

Omeprazole, the first proton pump inhibitor, is a category C drug. This drug has been shown to produce dose-related embryonic and fetal mortality in pregnant rats and rabbits administered doses similar to those for humans. However, several prospective database studies have shown the safety of omeprazole. The incidence of major abnormalities in pregnant women exposed to omeprazole was 5.1%, compared with 3.1% for those taking H_2 blockers and 3.0% for the untreated group. Because of the paucity of data about their effects, proton pump inhibitors are not recommended for mothers who are breastfeeding.

Lansoprazole

Lansoprazole is a category B drug. In 1 nonobservational cohort study, 6 pregnant patients exposed to lansoprazole during the first trimester delivered 7 healthy newborns. The relative risk for a congenital malformation was 1.6 (95% CI, 0.1-5.2), and for low birth weight, it was 1.8 (95% CI, 0.2-13.1).

Pantoprazole

Pantoprazole is also a category B drug. In a European cohort study, 53 pregnant women were exposed to pantoprazole, and the rate observed for congenital anomalies was 2.1%. Although the newer proton pump inhibitors rabeprazole and esomeprazole are also category B drugs, no controlled data are available about them; thus, their use is not recommended during pregnancy.

Esomeprazole

Esomeprazole is a category B drug. Most of its safety data come from studies done with its isomer, omeprazole. The single study that used esomeprazole showed a nonsignificant increase in the incidence of birth defects when the drug was used 4 weeks before pregnancy or in the first trimester.

Dexlansoprazole

Dexlansoprazole is a category B drug as well. To date, no controlled studies have been performed with humans. In reproductive studies with rodents given up to 40 times the recommended human dose, there was no evidence of adverse events.

Rabeprazole

Compared with studies of other proton pump inhibitors, rabeprazole studies have the least amount of human data. Studies with rodents given doses considered supra-therapeutic for humans did not show any increase in adverse events. Thus, rabeprazole is a category B drug.

Peptic Ulcer Disease

Treatment of peptic ulcer disease involves the use of proton pump inhibitors or H_2 blockers, which are discussed above in the Gastroesophageal Reflux Disease section. If peptic ulcer disease is related to *Helicobacter pylori* infection, treatment of the infection can be deferred until after pregnancy. The most common regimen involves triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Alternatively, metronidazole, bismuth, and tetracycline may be used if needed. In the unusual case when treatment is warranted during the gravid period, tetracycline and bismuth should not be used.

Amoxicillin

Amoxicillin is a category B drug. A population-based study of 401 women treated with amoxicillin did not show any increased risk of congenital malformation or any other adverse event compared with pregnant women not treated with amoxicillin.

Clarithromycin

Clarithromycin, a category C drug, has a higher rate of placental passage than other macrolide antibiotics. In a prospective study of clarithromycin in pregnancy, no increased risk of congenital malformations was reported; however, the rate of spontaneous abortions was higher than in the unexposed group. A retrospective surveillance study of clarithromycin exposure within 270 days of delivery showed no increase in congenital malformations, compared with that of the general population of pregnant women.

Tetracycline

Tetracycline, a category D drug, is possibly unsafe during lactation. It is discussed below in the Infectious Diarrhea section.

Metronidazole

Metronidazole is a category B drug and carries a low risk during lactation. It is discussed below in the Infectious Diarrhea section.

Bismuth

Bismuth, a category C drug, is one of the most commonly used over-the-counter antacids. Fetotoxicity from bismuth has been described for animals. Exposure to bismuth subsalicylate during late pregnancy may increase the risk of closure or constriction of the fetal ductus arteriosus, resulting in pulmonary hypertension. Bismuth is considered as possibly unsafe during lactation.

Acute and Chronic Pancreatitis

Acute pancreatitis often resolves with supportive care. If analgesia is required, meperidine and fentanyl are the preferred medications (discussed above in the Endoscopy section). If the patient cannot tolerate nutrition by mouth because of ongoing pain or ileus, early enteral feedings are recommended.

Chronic pancreatitis is managed with alcohol cessation, small low-fat meals, analgesia, and pancreatic enzyme supplements. Pancreatic enzymes are a category C drug because animal reproduction studies have not been performed. The data on safety during pregnancy and lactation are limited. Generally, unless these medications are essential, their use should be avoided. However, in patients with cystic fibrosis and pancreatic insufficiency, maintenance of nutritional status is a critical factor in pregnancy outcome. In a study of 23 women with 33 pregnancies, 91% of the women received pancreatic supplementation during pregnancy. The severity of lung disease predicted preterm delivery, and no congenital malformations were noted.

Biliary Tract Disease

Cholecystitis and Choledocholithiasis

Laparoscopic cholecystectomy has become the standard of care for the management of cholecystitis and symptomatic choledocholithiasis. Surgical intervention during pregnancy does not appear to be associated with an increase in complications, and if cholecystectomy is indicated during pregnancy, the second trimester is the best time. Nonsurgical approaches, such as oral chenodeoxycholic acid, oral ursodiol (ursodeoxycholic acid [UDCA]), and extracorporeal shock wave lithotripsy, have not been used in pregnancy and are not recommended. Chenodeoxycholic acid and UDCA have been used with limited success in the treatment of cholesterol gallstones in the general population. No data are available about chenodeoxycholic acid in pregnancy (UDCA is discussed below with primary sclerosing cholangitis).

Primary Sclerosing Cholangitis

There is no effective medical therapy for primary sclerosing cholangitis. The medication that has been used most commonly is UDCA, a category B drug. Its safety during lactation is not known. Human fetotoxicity from UDCA has not been reported; however, the data are not sufficient to determine risk in the first trimester. Therapeutic trials with UDCA have yielded inconsistent results, and high doses (25-30 mg/kg daily) may actually be harmful and should be avoided. UDCA can be administered during pregnancy, especially after the first trimester, to reduce cholestasis and accompanying sequelae such as pruritus.

Diseases of the Liver

The use of medications for diseases of the liver, including liver transplant, is summarized in Table 21.5.

Viral Hepatitis

Hepatitis A is a self-limited condition, and the treatment of pregnant women is similar to that of nonpregnant women. Both the

Table 21.5. Medications Used in the Treatment of Diseases of the Liver

Drug	*FDA Category*	*Recommendations for Pregnancy*	*Recommendations for Breastfeeding*
Adefovir dipivoxil	C	Minimal data: no teratogenicity	No human data: probably compatible (hepatitis B)
Antithymocyte globulin	C	Human-specific agent	Safety unknown
Cyclosporine	C	Safest of immunosuppressants	Limited human data: potential toxicity
Interferon	C	Not recommended: defer treatment until after delivery	Limited human data: probably compatible
Lamivudine	C	Low risk	Contraindicated
Muromonab-CD3 (Orthoclone OKT3)	C	No pregnancy data but probably low risk	Contraindicated
Mycophenolate mofetil	C	Not recommended	Contraindicated
Nadolol	C: First trimester D: Second and third trimesters	Prolonged half-life, so use alternative Risk of IUGR in second or third trimester	Limited human data: potential toxicity
Penicillamine	D	Significant embryopathy If required, decrease dose to 250 mg daily 6 wk before delivery	No human data: potential toxicity
Propranolol	C: First trimester D: Second and third trimesters	Fetal bradycardia IUGR in second and third trimesters	Limited human data: potential toxicity
Ribavirin	X	Contraindicated Severe fetal neurotoxicity	No human data: potential toxicity
Sirolimus	C	Not recommended	No human data: potential toxicity
Tacrolimus	C	Use if mother's health mandates	Limited human data: potential toxicity
Trientine	C	Limited human data: alternative to penicillamine	No human data: potential toxicity
Ursodiol	B	Low risk Used for intrahepatic cholestasis of pregnancy	No human data: probably compatible

Abbreviations: FDA, US Food and Drug Administration; IUGR, intrauterine growth retardation.

inactivated vaccine against hepatitis A and postexposure immunoglobulin prophylaxis are safe to administer during pregnancy.

Hepatitis B infection carries a high rate of vertical transmission, and the indications to treat are much greater during pregnancy. The vaccine is safe to use. Passive and active immunization, given together, are very effective in preventing neonatal transmission, reducing the carrier state of infants born to women who test positive for hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) (carrier state decreases from 70% to 90% to almost zero).

Lamivudine

The FDA has classified lamivudine as a category C drug. For women with chronic hepatitis B, studies have documented the safety of lamivudine for continued treatment during pregnancy. Standard doses of lamivudine have been continued through pregnancy with a hepatitis B virus (HBV)-DNA seroconversion rate of 92%, with no reported complications or congenital abnormalities. In an earlier study, investigators treated 8 highly viremic women with 150 mg lamivudine in the third trimester of pregnancy in an attempt to prevent perinatal transmission of HBV infection. One child was delivered early because of intrauterine growth retardation. All but 1 woman had a significant decrease in HBV DNA levels before delivery, and vertical transmission occurred in only 1 child.

In the literature on human immunodeficiency virus, the Antiretroviral Pregnancy Registry contains 526 live births that were exposed to lamivudine during the first trimester, with a congenital defect rate of 1.7%. Of 1,256 live births, 25 had a history of exposure at anytime during pregnancy and showed a slightly higher rate, 2.5% (95% CI, 1.3-3.0), but this was not statistically higher than expected. Lamivudine is contraindicated during breastfeeding because it is excreted into milk in high concentrations.

Adefovir Dipivoxil

Adefovir dipivoxil is a category C drug. No adequate well-controlled studies have been conducted on the use of adefovir dipivoxil in pregnant women. This drug is indicated for the treatment of chronic hepatitis B in adults who have evidence of active viral replication and evidence of either persistent increase in the serum levels of aminotransferases or histologically active disease. During clinical trials with this agent, 16 pregnancies with known outcomes were reported. Ten women had a therapeutic abortion, 2 had a spontaneous abortion, 3 delivered healthy babies, and 1 delivered a live-born infant at 25 weeks' gestation who died 4 days later. Studies conducted with adefovir dipivoxil administered orally in doses up to 23 times that achieved in humans have not shown any embryotoxicity or teratogenicity in laboratory animals. No human studies have been performed on the use of this drug during lactation, and its use during lactation is not recommended.

Interferon

Interferon, a category C drug, is contraindicated during pregnancy because of its antiproliferative activity. When interferon was administered to pregnant rhesus monkeys, they had a statistically significant increase in the number of spontaneous abortions. No teratogenic effects were observed in this species when doses of 1 million to 25 million IU/kg daily were administered during the early to mid-fetal period. To date, only 27 pregnancies have been reported after exposure to interferon. The majority of these women were being treated for essential thrombocythemia and not hepatitis C infection. Premature delivery occurred in 15% and intrauterine growth retardation in 22% of the patients (6 of 27). A total of 8 children have been born to mothers receiving interferon who were thought to be at high risk for chronic hepatitis infection. For patients with chronic infection, it is prudent to delay treatment, and for women with active infection, interferon therapy still should be considered—with close and careful monitoring—only if the health of the mother mandates therapy. The treatment of hepatitis C with interferon in combination with ribavirin is contraindicated because of severe neurotoxicity in children younger than 2 years and because of its high potential for teratogenicity (see the Ribavirin section below).

Ribavirin

Ribavirin is an antiviral agent used in combination with interferon for the treatment of hepatitis C. It is a category X drug. A dose-related teratogenicity, as well as embryolethality, has been demonstrated in all animal species tested. Ribavirin is still present in human blood 4 weeks after dosing, and it is recommended that patients wait at least 3 months after any exposure to the drug before conception.

While there are several FDA-approved regimens for hepatitis C with sustained viral response, the indications for treatment during pregnancy are individualized. Overall, treatment is not recommended during pregnancy because the potential risks outweigh the benefits.

Wilson Disease

Penicillamine

Penicillamine, a category D drug, is a chelating agent that is first-line therapy for Wilson disease. Only a few reports are available about the outcome of pregnancies in women with Wilson disease. The largest recent case series is from India, where 59 pregnancies in 16 women were studied retrospectively. This group included 24 spontaneous abortions, 3 stillbirths, 2 terminations, and 30 successful pregnancies. The majority of the spontaneous abortions were in women who were not receiving therapy. Other case reports have documented severe embryopathy characterized by micrognathia, diffuse cutis laxa, and agenesis of the corpus callosum in addition to transient fetal myelosuppression. It is debated whether penicillamine therapy should be continued during pregnancy; various authors have disagreed on whether to use the agent and, if so, how much to administer.

Trientine

Trientine is a category C drug and is used if no other alternatives are appropriate to treat the mother's liver disease. This chelating agent is an alternative to penicillamine for use in Wilson disease. Because there are few other options, the benefit is thought to outweigh the risk.

Primary Biliary Cirrhosis

Ursodeoxycholic Acid

UDCA is a category B drug. Because of the paucity of data about its safety in the first trimester, its use during this time is

not recommended unless essential. It has been administered to women during the second and third trimesters with no deterioration of liver function noted. No fetal loss or unfavorable outcomes were noted among 10 women receiving the drug. In a randomized controlled trial of UDCA in intrahepatic cholestasis of pregnancy, UDCA was shown to improve pruritus and liver enzyme levels, and it allowed for delivery closer to term. A second randomized controlled trial of UDCA versus cholestyramine reported similar results: Symptoms were alleviated and babies were delivered significantly closer to term in the UDCA-treated patients.

Portal Hypertension

Propranolol

Propranolol, a category C drug in the first trimester, is a nonselective β-adrenergic blocking agent used for prophylaxis against variceal bleeding in patients with cirrhosis. It has been administered during pregnancy to treat maternal thyrotoxicosis, arrhythmias, and hypertension. It readily crosses the placenta and, thus, is used also to treat fetal arrhythmias. Adverse outcomes have not been clearly linked to its use, but daily doses greater than 160 mg appear to produce more serious fetal cardiac complications. No data have been reported for outcomes among women who took this drug for variceal prophylaxis. Propranolol is not a teratogen, but fetal and neonatal toxicity may occur. Maternal use after the second trimester can result in significant weight reductions in the infant. Therefore, it is not recommended for use after the first trimester unless the underlying condition of the mother requires continued β-blockade.

Nadolol

Nadolol, a category C drug in the first trimester, is another nonselective β-adrenergic blocker. It is an alternative to propranolol. Nadolol is used predominantly as an antihypertensive, and no data are available for its use for variceal prophylaxis. Because nadolol has a long half-life, low protein binding, and lack of metabolism, the use of alternative agents in this class is recommended if treatment is strongly indicated.

Liver Transplant

The best data available about medications for transplant recipients are from the National Transplantation Pregnancy Registry. Every year, an updated report is presented with the results from a prospective database of all transplant recipients. In a recent report, the rate of live births was 77% for women receiving cyclosporine other than Neoral, 82% for those receiving cyclosporine as Neoral, and 72% for those receiving tacrolimus. Two patients were receiving mycophenolate mofetil therapy and delivered healthy infants. The mean gestational age was 37 weeks, and the rate of low birth weight was 29% to 42%. The conclusion of the advisory board was that "the majority of pregnancy outcomes reported to the Registry appear favorable for parent and newborn."

Cyclosporine

Cyclosporine is a category C drug. A meta-analysis of 15 studies of pregnancy outcomes after cyclosporine therapy reported on a total of 410 patients. For major malformations, the calculated OR of 3.83 (95% CI, 0.75-19.6) did not achieve statistical significance. The rate of malformations, 4.1%, was not different from that of the general population. The conclusion from the study was that cyclosporine did not appear to be a major human teratogen. The American Academy of Pediatrics considers cyclosporine contraindicated during breastfeeding because of the potential for immunosuppression and neutropenia.

Tacrolimus

Tacrolimus is another category C drug. The earliest experience with this medication was in 1997, with a report of 27 pregnancies with exposure to tacrolimus. Another study from Germany reported on 100 pregnancies in transplant recipients followed from 1992 to 1998. The live birth rate was 68%, the spontaneous abortion rate 12%, and the stillbirth rate 3%; 59% of the infants were premature. Malformations occurred in 4 neonates, with no consistent defects. Tacrolimus is contraindicated during lactation because of the high concentrations found in breast milk.

Sirolimus

Sirolimus is a category C drug. Little is known about its effect in humans. Sirolimus is another agent used for immunosuppression in transplant recipients. Three patients in the National Transplantation Pregnancy Registry were treated with sirolimus, but they were kidney recipients. Because of the relative paucity of information, and the reasonable alternatives for immunosuppression, this agent is not recommended during pregnancy.

Mycophenolate Mofetil

Mycophenolate mofetil, a category C drug, has been shown to have teratogenic properties in laboratory animals. This drug is a relatively new agent for immunosuppression in liver transplant patients. In a single case report in the obstetric literature, a kidney transplant recipient was treated with mycophenolate mofetil before conception and during the first trimester of pregnancy. The fetus had facial dysmorphology and multiple midline anomalies. The molecular weight of this agent is low enough that it most likely crosses the placenta. It is not recommended for use in pregnancy. The manufacturer recommends that women use effective contraception before and during therapy and for 6 weeks after therapy has stopped.

Irritable Bowel Syndrome

Irritable bowel syndrome is a heterogeneous disorder without a standardized therapeutic regimen. No large epidemiologic studies have been conducted with pregnant women who have preexisting irritable bowel syndrome. If possible, medications should be avoided and dietary alterations and fiber supplementation should be the first step for complaints of constipation. The following is a summary of available safety data about drugs for irritable bowel syndrome should medication be required. Note that most drug therapies for the treatment of this syndrome have not demonstrated efficacy over placebo. The use of medications for irritable bowel syndrome during pregnancy is summarized in Table 21.6.

Constipation

For a pregnant woman with constipation, first-line therapy should be fiber supplements, introduced gradually to avoid excessive gas and bloating, and adequate water intake. Often, new-onset constipation during early pregnancy is due to iron therapy, and symptomatic relief can be achieved with docusate, now a component of

Table 21.6. Medications Used in the Treatment of Irritable Bowel Syndrome

Drug	*FDA Category*	*Recommendations for Pregnancy*	*Recommendations for Breastfeeding*
Alosetron	B	Avoid: restricted access	No human data: potential toxicity
Amitriptyline	C	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Bisacodyl	C	Safe with short-term use	Safety unknown
Bismuth subsalicylate	C	Not safe: teratogenicity	No human data: potential toxicity
Castor oil	X	Uterine contraction and rupture	Possibly unsafe
Cholestyramine	C	Low risk, but can lead to infant coagulopathy	Compatible
Desipramine	C	Avoid: no malformations, but worse outcome	Limited human data: potential toxicity
Dicyclomine	B	Avoid: possible congenital anomalies	Limited human data: potential toxicity
Diphenoxylate-atropine	C	Teratogenic in animals; no human data	Limited human data: potential toxicity
Docusate	C	Safe	Compatible
Hyoscyamine	C	No available data	No human data: probably compatible
Imipramine	D	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Kaopectate (bismuth subsalicylate)	C	Unsafe; now contains bismuth subsalicylate	No human data: probably compatible
Lactulose	B	No human studies	No human data: probably compatible
Loperamide	B	Low risk: possibly increased cardiovascular defects	Limited human data: probably compatible
Lubiprostone	C	Limited human data: use when benefit outweighs risk	No human data: not recommended
Magnesium citrate	B	Avoid long-term use: hypermagnesemia, hyperphosphatemia, dehydration	Compatible
Mineral oil	C	Avoid: neonatal coagulopathy and hemorrhage	Possibly unsafe
Nortriptyline	D	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Paroxetine	D	Avoid: twice as many birth defects as other antidepressants	Potential toxicity
Polyethylene glycol	C	First-choice laxative in pregnancy	Low risk
Senna	C	Safe with short-term use	Compatible
Selective serotonin reuptake inhibitors (except paroxetine)	C	Avoid: no malformations, but increased adverse fetal events	Limited human data: potential toxicity
Simethicone	C	No available data Low risk	No human data: probably compatible
Sodium phosphate	None	Avoid long-term use: hypermagnesemia, hyperphosphatemia, dehydration	Safety unknown
Tegaserod	B	Low risk: human data negative for malformations	Safety unknown

Abbreviation: FDA, US Food and Drug Administration.

some prenatal vitamins. When these methods are inadequate, an osmotic laxative should be considered, particularly a polyethylene glycol solution. Osmotic laxatives include saline osmotics (magnesium and sodium salts), saccharated osmotics (lactulose and sorbitol), and polyethylene glycol. Saline osmotic laxatives such as magnesium citrate (category B) and sodium phosphate have rapid onset of action but are intended for short-term intermittent relief. Long-term use can result in hypermagnesemia, hyperphosphatemia, and dehydration. No human studies are available on the use of lactulose (category B) during pregnancy. Polyethylene glycol (category C) is negligibly absorbed and metabolized in humans, making it unlikely to cause malformations. Also, it is effective and well tolerated compared with lactulose. The results of animal teratogenesis studies have been negative. A consensus meeting on the management of constipation in pregnancy considered polyethylene glycol to meet the criteria for an ideal laxative in pregnancy: effective, not absorbed (nonteratogenic), well tolerated, and safe. However, the consensus members thought that current data were insufficient to demonstrate conclusively whether absorption of polyethylene glycol affects the fetus.

Stimulant laxatives such as senna (category C) and bisacodyl (category C) are considered safe for short-term use, but long-term use is not recommended. Because senna is excreted in breast milk, it should be used with caution during lactation. Docusate (category C), a stool softener, is generally considered safe. Castor oil (category X) should be avoided because it is associated with uterine contraction and rupture. Mineral oil also should be avoided because it can impair maternal fat-soluble vitamin absorption, leading to neonatal coagulopathy and hemorrhage.

Tegaserod (category B), a serotonin 5-hydroxytryptamine$_4$ receptor agonist, was approved by the FDA for the treatment of constipation-type irritable bowel syndrome and chronic constipation. It was withdrawn from the market in 2007 because of concern about an increased risk of cardiac events with its use.

Lubiprostone was recently approved by the FDA to treat chronic constipation and constipation-predominant irritable bowel syndrome. It is a category C drug with limited human data. It is not recommended for use when breastfeeding.

Diarrhea

In a trial of 105 women exposed to loperamide (category B) during pregnancy, loperamide was not found to be associated with an increased risk of congenital malformations, although 20% of the infants were 200 g smaller than infants in the control group. At least 187 cases of first-trimester exposure have been reported, with no evidence of developmental toxicity. Cholestyramine (category C), an anion exchange resin, is often used to treat cholestasis of pregnancy and can be used to manage diarrhea resulting from ileal resection or cholecystectomy. However, fat-soluble vitamin deficiency, including coagulopathy, can occur, so it should be used with caution. Kaolin in combination with pectin (Kaopectate) (category B) was an antidiarrheal of choice because it was not absorbed and did not cross the placenta, but concern arose over the potential for kaolin-induced iron deficiency anemia. In 2003, Kaopectate was reformulated to contain bismuth subsalicylate (category C). Bismuth subsalicylate, alone or in Kaopectate, should be avoided in pregnancy because the

salicylates can be absorbed and lead to increased perinatal mortality, premature closure of the ductus arteriosus, neonatal hemorrhage, decreased birth weight, prolonged gestation and labor, and possible teratogenicity. Alosetron (category B) has restricted access because of concern about ischemic colitis. It generally should be avoided during pregnancy.

For pregnant women with diarrhea, dietary modification, with reduction of fats and dairy, can improve symptoms. Although human data are limited, both loperamide and diphenoxylate (not diphenoxylate-atropine) are considered "low risk" and can be used with discretion.

Tricyclic antidepressants (amitriptyline and desipramine, both category C drugs, and nortriptyline and imipramine, both category D drugs) and selective serotonin reuptake inhibitors (SSRIs) (generally category C drugs) are frequently used in the management of irritable bowel syndrome. Overall, the newer antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, reboxetine, venlafaxine, nefazodone, trazodone, mirtazapine, and bupropion) are not associated with an increased rate of major malformations compared with that of the general population. Recently, however, an unpublished GlaxoSmithKline study of 3,500 pregnant women noted twice as many birth defects with paroxetine than with other antidepressants (Table 21.6). In the first trimester, for paroxetine users the absolute rate of major congenital malformations was 4% and the absolute rate of cardiovascular malformations was 2%. Infants exposed to antidepressants are also at higher risk for other adverse events. A large Swedish study of 997 infants exposed to antidepressants during pregnancy noted an increased risk of preterm birth, low birth weight, low Apgar score, respiratory distress, neonatal convulsions, and hypoglycemia. There was a trend toward worse outcome with tricyclic antidepressants compared with SSRIs. Multiple studies with SSRIs have confirmed that the rate of congenital malformations for infants exposed to these drugs is similar to that for the general population; however, the studies also have noted a higher rate of premature delivery, respiratory difficulty, cyanosis on feeding, and jitteriness as well as low birth weight and neonatal convulsions for SSRI groups of infants. The effect of SSRI exposure through the placenta on neonatal adaptation and long-term neurocognitive development is debated. If the antidepressant is being administered solely to treat symptoms of irritable bowel syndrome and not an associated major depression, strong consideration should be given to stopping the drug therapy during the gravid period.

Antispasmodics are prescribed frequently for the management of abdominal pain in irritable bowel syndrome. Dicyclomine (category B), in combination with pyridoxine and doxylamine (Diclergis), has been associated with multiple congenital anomalies, but the studies have not been conclusive. Hyoscyamine (category C) has not been studied in pregnancy.

Infectious Diarrhea

Diarrhea can be described as acute (≤14 days), persistent (>14 days), or chronic (>30 days). Although most episodes of diarrhea are self-limited and treatment is not required, certain pathogens require treatment. The common medications used to treat infectious diarrhea are summarized in Table 21.7.

Albendazole

Albendazole, a category C drug, is used in the treatment of microsporidia infection, cysticercosis, helminth infection, and hydatid disease. The drug is embryotoxic and teratogenic (skeletal malformations) in rats and rabbits. Human data are limited. Albendazole therapy for the eradication of helminths during pregnancy is associated with significantly less maternal anemia and no increase in adverse pregnancy outcomes, prompting the World Health Organization to recommend antihelminthic therapy in pregnancy.

Ampicillin

Ampicillin, a category B drug, is not considered teratogenic. It is second-line treatment of *Shigella* infection. Ampicillin passes through the placenta by simple diffusion and is excreted into breast milk in low concentrations.

Table 21.7. Medications Used for the Treatment of Infectious Diarrhea

Drug	*FDA Category*	*Recommendations for Pregnancy*	*Recommendations for Breastfeeding*
Albendazole	C	Embryotoxic in animals Avoid in first trimester Human data support improved pregnancy outcomes with helminth eradication	No human data: probably compatible
Ampicillin	B	Safe	Compatible
Azithromycin	B	Low risk	Limited human data: probably compatible
Ciprofloxacin (all quinolones)	C	Potential toxicity to cartilage: avoid	Limited human data: probably compatible
Doxycycline	D	Contraindicated: teratogenic	Compatible
Fidaxomicin	B	Low risk but expensive	No human data: potential toxicity
Furazolidone	C	Low risk Limited data	No human data: potential toxicity
Metronidazole	B	Low risk: question of increased risk of cleft lip with or without cleft palate	Limited human data: potential toxicity
Rifaximin	C	Animal teratogen No human data	No human data: probably compatible
Tetracycline	D	Not safe: teratogenicity	Compatible
Tinidazole	C	Low risk Limited data	Unsafe
Trimethoprim-sulfamethoxazole	C	Teratogenic	Compatible
Vancomycin	C	Low risk	Limited human data: probably compatible

Abbreviation: FDA, US Food and Drug Administration.

Azithromycin

Azithromycin, a macrolide antibiotic, is in pregnancy category B and is a second-line treatment of *cryptosporidium* and *Entamoeba histolytica* infections. In pregnant women with traveler's diarrhea, azithromycin or a third-generation cephalosporin is considered the treatment of choice. A study of 20 women who received the drug for *Chlamydia trachomatis* infection noted that 40% complained of moderate to severe gastrointestinal side effects. A trial of 94 pregnant women with *Trichomonas vaginalis* treated with a combination of azithromycin, cefixime, and metronidazole demonstrated increased rates of infant low birth weight, preterm birth, and 2-year mortality compared with rates for the children of 112 infected mothers who were not treated for the same infection.

Doxycycline and Tetracycline

Doxycycline and tetracycline are both category D drugs. Doxycycline is used as second-line treatment of infections with *Vibrio cholerae, Campylobacter*, and enterotoxigenic *Escherichia coli*. Similar to tetracycline, this class of medications crosses the placenta and is bound by chelating with calcium in developing bone and teeth. This results in discoloration of the teeth, hypoplasia of enamel, and inhibition of skeletal growth. A population-based study found a higher rate of congenital anomalies in the infants of mothers who used doxycycline during pregnancy; however, the case-control pair analysis did not show a significantly higher rate of doxycycline treatment in the second and third months of gestation in any group of congenital abnormalities.

Fidaxomicin

Fidaxomicin, a category B drug, recently received FDA approval for treatment of *C difficile* infection. Its use is limited by its cost, and it has not been studied in large numbers of pregnancies to date.

Furazolidone

Furazolidone, a category C drug, is second-line treatment of giardiasis. Few data are available on the safety of furazolidone in pregnancy, but the Collaborative Perinatal Project monitored 50,282 mother-child pairs and 132 had exposure to furazolidone in the first trimester with no association with congenital malformations.

Metronidazole

Metronidazole, a category B drug, is used to treat *C difficile* infection, amebiasis, and giardiasis. Multiple studies have suggested that exposure to metronidazole prenatally is not associated with birth defects. These studies include 2 meta-analyses, 2 retrospective cohort studies, and a prospective controlled study of 228 women exposed to metronidazole during pregnancy. A population-based case-control study found that overall teratogenic risk was low, but infants of women exposed to metronidazole in the second to third months of pregnancy had higher rates of cleft lip, with or without cleft palate. This increase was slight and not thought to be clinically significant.

Quinolones

Quinolones (eg, ciprofloxacin, levofloxacin, and norfloxacin), category C drugs, are used to treat infections with *Shigella, Campylobacter, Yersinia*, entertoxigenic and enteroinvasive *E coli*, and *V cholerae*. Quinolones have a high affinity for bone tissue and cartilage and may cause arthropathies in children. The manufacturer reports damage to cartilage in weight-bearing joints after quinolone exposure in immature rats and dogs. However, a prospective controlled study of 200 women exposed to quinolones and a population-based cohort study of 57 women exposed to quinolones did not find an increased risk of congenital malformations. Overall, the risk is thought to be minimal, but because safer alternatives are available, quinolones should be avoided in pregnancy.

Rifaximin

Rifaximin, a category C drug, can be used to treat traveler's diarrhea, although azithromycin is the antibiotic of choice for pregnant patients with traveler's diarrhea. Little information exists about the safety of rifaximin in pregnancy. Rifaximin has not been found to affect fertility or pregnancy outcome in rats or, in 1 study, to cause teratogenic complications in rats and rabbits. However, other studies have noted teratogenicity in rats and rabbits, including cleft palate and incomplete ossification.

Tinidazole

Tinidazole, a category C drug, is a second-line treatment of giardiasis and amebiasis. Placental transfer of tinidazole occurs early in pregnancy, raising concern about its use in the first trimester. A population-based study from Hungary did not note an increased rate of congenital malformations when the drug was administered during pregnancy; however, the number of women treated with tinidazole was small.

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole, a category C drug, is first-line treatment of infections with *Cystoisospora* (previously known as *Isospora*) or *Cyclospora* and second-line treatment of infections with *Shigella, Yersinia*, or enterotoxigenic *E coli*. Trimethoprim has antifolate effects, increasing the potential of congenital anomalies. A study of 2,296 Michigan Medicaid recipients with first-trimester exposure to trimethoprim noted an increased risk of birth defects, particularly cardiovascular defects. A population-based case-control study in Hungary noted a higher rate of multiple congenital anomalies and cardiovascular malformations. On the basis of these data, use of trimethoprim-sulfamethoxazole should be avoided in pregnancy.

Vancomycin

Vancomycin, a category C drug, is used in the treatment of severe *C difficile* colitis, or *C difficile* infection that is refractory to treatment with metronidazole. Studies in rats and rabbits have not demonstrated teratogenic effects. No cases of congenital defects attributable to vancomycin have been located, and the drug is considered low risk in pregnancy.

Inflammatory Bowel Disease

For patients with Crohn disease and ulcerative colitis, disease activity at the time of conception can be associated with a higher risk of spontaneous abortion, and disease activity during the course of pregnancy can be associated with higher rates of low

Table 21.8. Medications Used in the Treatment of Inflammatory Bowel Disease (IBD)

Drug	*FDA Category*	*Recommendations for Pregnancy*	*Recommendations for Breastfeeding*
Adalimumab	B	Limited human data: low risk	No human data: probably compatible
Amoxicillin-clavulinic acid	B	Low risk	Probably compatible
Azathioprine and 6-mercaptopurine	D	Data in IBD and transplant literature suggest low risk	No human data: potential toxicity
Balsalazide	B	Low risk	No human data: potential diarrhea
Certolizumab pegol	B	Low risk	No human data
Ciprofloxacin	C	Avoid: potential toxicity to cartilage	Limited human data: probably compatible
Corticosteroids	C	Low risk: possibly increased risk of cleft palate, adrenal insufficiency, premature rupture of membranes	Compatible
Cyclosporine	C	Low risk	Limited human data: potential toxicity
Fish oil supplements	None	Safe Possible benefit	No human data
Infliximab	B	Low risk	No human data: probably compatible
Mesalamine	B	Low risk	Limited human data: potential diarrhea
Methotrexate	X	Contraindicated: teratogenic	Contraindicated
Metronidazole	B	Avoid: limited efficacy in IBD and risk of cleft palate	Limited human data: potential toxicity
Natalizumab	B	Low risk	No human data
Olsalazine	C	Low risk	Limited human data: potential diarrhea
Rifaximin	C	Animal teratogen No human data	No human data: probably compatible
Sulfasalazine	B	Considered safe Give folate 2 mg daily	Limited human data: potential diarrhea
Tacrolimus	C	Use if mother's health mandates	Limited human data: potential toxicity
Thalidomide	X	Contraindicated: teratogenic	No human data: potential toxicity

Abbreviation: FDA, US Food and Drug Administration.

birth weight and premature infants. It is advisable that patients be in remission when considering pregnancy, and for the majority, this requires continuing the medications. Medications used to treat inflammatory bowel disease are summarized in Table 21.8.

Aminosalicylates

All aminosalicylates (sulfasalazine, mesalamine, and balsalazide) are category B drugs except olsalazine, and the mesalamine products Asacol and Asacol HD, which are category C. A population-based study using the Hungarian Case-Control Surveillance of Congenital Abnormalities database did not show a significant increase in the prevalence of congenital abnormalities in the children of women treated with sulfasalazine. Because of concern about potential antifolate effects of sulfasalazine, it is recommended that women take folic acid 1 mg twice daily in the prenatal period and throughout pregnancy. Unlike with other sulfonamides, bilirubin displacement and, thus, kernicterus do not occur in the infant. Sulfasalazine has been clearly associated with infertility in men. Abnormalities in sperm number, motility, and morphology have been noted. This effect appears to be reversible: When mesalamine was substituted for sulfasalazine, semen quality returned to normal. An association has been described between sulfasalazine use in the parent and congenital malformations in the progeny. Because the lifespan of sperm is 120 days, men considering conception should either stop taking sulfasalazine or switch to mesalamine at least 3 months before attempting conception.

Case series of mesalamine use in pregnancy do not suggest an increased risk to the fetus. This has been supported by a prospective controlled trial of 165 women exposed to mesalamine who were compared with matched controls with no exposure and by a population-based cohort study from Denmark. However, recently the FDA changed the rating for Asacol and Asacol HD because the coating on these particular agents contains dibutyl phthalate, a chemical associated with urogenital malformations in male offspring. The amounts given to rodents were 40 times that of therapeutic doses in humans, but because of the lack of controlled safety data, the labeling was changed.

Antibiotics

Metronidazole, the quinolones, and rifaximin are covered in the Infectious Diarrhea section above. Because of the limited evidence of the effectiveness of these agents in treating inflammatory bowel disease and the extended duration of use in the treatment of Crohn disease and ulcerative colitis, use of these drugs should be avoided during pregnancy. Short courses for the treatment of pouchitis can be considered on the basis of the safety data presented above. An alternative antibiotic for pouchitis is amoxicillin-clavulanic acid, a category B drug.

Corticosteroids

Corticosteroids are category C drugs. A case-control study of corticosteroid use during the first trimester of pregnancy noted an increased risk of oral clefts in newborns. This was confirmed by a large case-control study and a meta-analysis, which reported a summary OR for case-control studies examining the risk of oral clefts (OR, 3.35; 95% CI, 1.97-5.69). However, the population was treated for various conditions, and the overall risk of major malformations was low (OR, 1.45; 95% CI, 0.80-2.60). A prospective controlled study of 311 women who received corticosteroids during the first trimester did not note an increased rate of major anomalies, and cases of oral cleft were not noted. The study was powered to find a 2.5-fold increase in the overall rate of major anomalies. An increased risk of premature rupture of membranes and adrenal insufficiency in the newborn has been reported for transplant patients. Overall, the use of corticosteroids poses a small risk to the developing infant, and the mother needs to be informed about the benefits and risks of therapy. A small retrospective review of patients with inflammatory bowel disease

treated with budesonide during pregnancy did not document congenital malformations or an increase in adverse outcomes.

Bisphosphonates

The bisphosphonates alendronate and risedronate are category C drugs. Their safety in breastfeeding is not known. For many patients, treatment of inflammatory bowel disease starts with these medications in conjunction with corticosteroids to prevent bone loss. Both agents should be avoided in pregnancy because animal studies have shown that alendronate crosses the placenta and is stored in fetal bone, causing anatomical changes. The effects on human fetal bone development are not known. The half-life of alendronate is longer than 10 years, and it accumulates in bone. The concern with giving this agent to a woman of childbearing potential is that the drug is released slowly from bone and may produce low-level, continuous exposure to the fetus throughout gestation. Risedronate has a half-life of 20 days and may be the better choice for a woman contemplating future pregnancy. However, 5 half-lives of the drug are needed to excrete 97% of it, so women should wait at least 100 days from the last dose before considering conception.

Immunomodulators

The immunomodulators are the most controversial agents used to treat inflammatory bowel disease in pregnant women.

Methotrexate

Methotrexate, a category X drug, is clearly teratogenic and should not be administered to women or men who are considering conception. Methotrexate is a folic acid antagonist, and its use during the critical period of organogenesis (6-8 weeks postconception) is associated with multiple congenital anomalies collectively called *methotrexate embryopathy* or *fetal aminopterin-methotrexate syndrome*. This syndrome is characterized by intrauterine growth retardation; decreased ossification of the calvarium; hypoplastic supraorbital ridges; small, low-set ears; micrognathia; limb abnormalities; and, occasionally, mental retardation. Exposure in the second and third trimesters may be associated with fetal toxicity and mortality. Methotrexate may cause reversible oligospermia in men. No case reports have been published on congenital anomalies occurring in the offspring of men receiving methotrexate therapy. Methotrexate may persist in tissues for long periods, and it has been suggested that patients wait at least 3 to 6 months after discontinuation of treatment with the drug before attempting conception.

Azathioprine and 6-Mercaptopurine

The drug 6-mercaptopurine and its prodrug azathioprine are in category D. Animal studies have demonstrated teratogenicity, with increased frequencies of cleft palate and open-eye and skeletal anomalies in mice exposed to azathioprine and cleft palate and skeletal and urogenital anomalies in rats. Transplacental and transamniotic transmission of azathioprine and its metabolites from the mother to the fetus can occur. The oral bioavailability of azathioprine (47%) and 6-mercaptopurine (16%) is low, and the early fetal liver lacks the enzyme inosinate pyrophosphorylase, which is needed to convert azathioprine to 6-mercaptopurine. Both features may protect the fetus from toxic drug exposure during the crucial period of organogenesis. The largest evidence on safety comes from transplant studies, in which rates of anomalies ranged from zero to 11.8%, and no evidence emerged for recurrent patterns of congenital anomalies. Multiple case series of inflammatory bowel disease have not noted an increase in congenital anomalies. On the basis of the large experience with transplant patients and the body of evidence in inflammatory bowel disease, the drugs are often continued during pregnancy to maintain remission in the mother. A flare of disease during pregnancy may be more deleterious to neonatal outcome than any potential risk from the medication.

Cyclosporine and Tacrolimus

These agents are considered in the Liver Transplant section. For severe steroid-refractory ulcerative colitis, cyclosporine may be a better treatment option than colectomy, which is associated with a considerable morbidity rate for mother and fetus.

Thalidomide

Thalidomide, a category X drug, has some anti–tumor necrosis factor effects and has been used successfully for the treatment of Crohn disease. However, its teratogenicity has been documented extensively and includes limb defects, central nervous system effects, and abnormalities of the respiratory, cardiovascular, gastrointestinal, and genitourinary systems. Thalidomide is contraindicated during pregnancy and for women of childbearing age who are not using 2 reliable methods of contraception for 1 month before starting therapy, during therapy, and for 1 month after stopping therapy.

Biological Therapy

Infliximab

Infliximab, a category B drug, is used in the management of Crohn disease and ulcerative colitis. A growing body of evidence suggests that infliximab is low risk in pregnancy. The 2 largest studies are from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) Registry and the infliximab safety database maintained by Janssen Biotech, Inc. The TREAT Registry is a prospective registry of patients with Crohn disease, and the patients may or may not be treated with infliximab. Among the 5,807 patients enrolled, 66 pregnancies were reported, and 36 of the 66 had prior exposure to infliximab. Fetal malformations did not occur in any of the pregnancies. The rates of miscarriage (11.1% vs 7.1%, P=.53) were neonatal complications (8.3% vs 7.1%, P=.78) were not significantly different between infliximab-treated and infliximab-naive patients, respectively.

In the infliximab safety database, a retrospective data collection, pregnancy outcome data are available for 96 women who had direct exposure to infliximab. The 96 pregnancies resulted in 100 births. The expected outcomes and the observed outcomes for women exposed to infliximab were not different from those of the general population. In a series of 10 women who received maintenance therapy with infliximab throughout pregnancy, all 10 pregnancies ended in live births and no congenital malformations were reported.

Infliximab probably crosses the placenta, beginning at approximately week 20. Currently, if maternal health warrants infliximab therapy, it is continued through pregnancy.

Adalimumab

Adalimumab, a category B drug, has been shown recently to be safe and effective for the induction of remission in Crohn

disease. A case report has documented a successful pregnancy in a woman with long-standing Crohn disease who began treatment with adalimumab 1 month before conception and received a total of 38 doses during her pregnancy. It is unclear whether the drug crosses the placenta, but it is assumed to do so, starting at about week 20. Adalimumab therapy during pregnancy is warranted for active disease or maintenance of remission.

Certolizumab Pegol

Certolizumab is a pegylated Fab′ fragment of IgG1 antibody against tumor necrosis factor α. Studies have shown the lack of placental transfer of certolizumab, and it may thus have an advantage for use in pregnancy. Certolizumab pegol therapy is warranted during pregnancy for active inflammatory bowel disease or maintenance of remission.

Natalizumab

Natalizumab is a monoclonal antibody of the IgG4 class directed against α integrins. On the basis of animal and trial data, it is listed as an FDA category B drug. Few postmarketing data are available about its use in pregnancy. Currently, there are no firm recommendations about its use in treating inflammatory bowel disease in pregnant women.

Fish Oil Supplements

Many patients who have inflammatory bowel disease take fish oil supplements as an adjunct to standard medical therapy. Because fish oil is a supplement and not a drug, it is not rated by the FDA. A randomized controlled trial of fish oil supplementation showed a prolongation of pregnancy without detrimental effects on the growth of the fetus or the course of labor. Fish oil supplementation may help prevent miscarriage associated with the antiphospholipid antibody syndrome. In women with inflammatory bowel disease who may be at increased risk for preterm birth and miscarriage, fish oil supplementation is not harmful and may be of some benefit.

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Questions and Answers

Questions

Abbreviations used:

5-ASA, 5-aminosalicylate
ALT, alanine aminotransferase
ANCA, antineutrophil cytoplasmic antibody
ASCA, anti–*Saccharomyces cerevisiae* antibody
AST, aspartate aminotransferase
cGMP, cyclic guanosine monophosphate
COX-2, cyclooxygenase 2
CT, computed tomography
DEXA, dual energy x-ray absorptiometry
D-IBS, diarrhea-predominant irritable bowel syndrome
EGFR, epidermal growth factor receptor
FDA, US Food and Drug Administration
GC-C, guanylate cyclase-C
IBD, inflammatory bowel disease
IBS, irritable bowel syndrome
IBS-C, constipation-predominant irritable bowel syndrome
INR, international normalized ratio
MR, magnetic resonance
MRI, magnetic resonance imaging
NSAID, nonsteroidal antiinflammatory drug
PI-IBS, postinfectious irritable bowel syndrome
PNTML, pudendal nerve terminal motor latency
PPD, purified protein derivative (tuberculin)
PPI, proton pump inhibitor
PSC, primary sclerosing cholangitis
SEER, Surveillance, Epidemiology, and End Results
TNF, tumor necrosis factor
TPMT, thiopurine methyltransferase
VEGF, vascular endothelial growth factor
WBC, white blood cell

Multiple Choice (choose the best answer)

V.1. **A 22-year-old woman presents with a 6-week history of bloody diarrhea. Symptoms began after she returned from a 1-week vacation in Mexico. She reports a 4.5-kg weight loss over the past 6 weeks. She has 1 or 2 nocturnal stools, with 6 to 8 bowel movements during the day, and experiences urgency 30 minutes after meals. She has abdominal pain that is relieved by the passage of stool, and she has intermittent bloating without nausea or vomiting. She uses NSAIDs once or twice weekly for headaches, but she has not used antibiotics recently. There is no family history of IBD. She is sexually active. Which of the following is *not* a reasonable next step?**

a. Urine pregnancy test
b. Stool culture
c. Stool assessment for *Clostridium difficile* toxin
d. Colonoscopy
e. Loperamide before meals

V.2. **An 18-year-old woman presents to your office with her parents. She recently received a diagnosis of ileocolonic Crohn disease while attending an out-of-state university. She provides records that include a colonoscopy report describing patchy colonic inflammation, rectal sparing, and severe ileitis. Biopsy specimens from the ileum and colon showed chronic inflammatory changes with noncaseating granulomas. Which of the following statements is correct?**

a. Crohn disease patients are not at an increased risk of colon cancer
b. Noncaseating granulomas are suggestive of ulcerative colitis
c. ASCA and ANCA testing needs to be performed to confirm the diagnosis
d. In patients with Crohn disease, penetrating complications such as fistulas can develop

e. Most patients are older than 30 years when they receive a diagnosis

V.3. A 28-year-old man with established pancolonic ulcerative colitis presents with increased frequency of bowel movements over the past week. His stool frequency, 1 or 2 bowel movements daily at baseline, has increased to 2 to 4 daily. He reports no hematochezia, nocturnal stools, abdominal pain, weight loss, or recent antibiotic use. He had been in clinical remission with 5-ASA therapy for the past 4 years. He denies missing any doses of his medication. Which of the following is the most appropriate next step?

a. Start corticosteroid therapy
b. Change to a different 5-aminosalicylic acid agent
c. Test the stool for *Clostridium difficile* toxin
d. Recommend colonoscopy
e. Recommend CT enterography

V.4. A 36-year-old man with a history of Crohn ileocolitis is referred for evaluation and management. He had an ileocecal resection 7 years ago. Over the past 2 months he has had increased fatigue, bloating, and 4 or 5 bowel movements daily (baseline, 2 or 3 daily). He asks why CT enterography has been ordered in addition to colonoscopy. Which of the following would be appropriate justification for CT enterography?

a. Cross-sectional imaging with CT enterography provides assessments of intestinal regions that may be inaccessible to standard endoscopic techniques
b. CT enterography can be used to diagnose penetrating disease
c. CT enterography can be used to detect extraintestinal manifestations
d. CT enterography has been shown to alter IBD management plans
e. All of the above

V.5. A 24-year-old woman with established Crohn ileitis presents for follow-up medical evaluation. She wants to become pregnant. Which of the following is true?

a. Methotrexate is believed to be safe with pregnancy if folic acid is coadministered
b. Fertility is reduced in all IBD patients
c. Women in remission before pregnancy are more likely to remain in remission during pregnancy
d. Pregnancy is contraindicated in patients with an ileostomy
e. IBD flares are most common in the third trimester

V.6. A 23-year-old man with newly diagnosed Crohn disease returns for follow-up. He was recently hospitalized and started corticosteroid therapy. He is now in clinical remission. He has been researching Crohn disease extensively on the Internet. Which of the following statements is correct?

a. Men have a higher overall incidence of Crohn disease
b. Crohn disease is historically more common than ulcerative colitis
c. IBD is uncommon among Ashkenazi Jews
d. Patients with IBD have no specific dietary restrictions
e. Ulcerative colitis is more common among smokers

V.7. A 24-year-old woman has a 4-year history of Crohn disease of the ileum, cecum, and ascending colon. The disease has been maintained in remission for the past year with infliximab. She now presents with fever, nausea, vomiting, and right lower quadrant pain, and she reports having 4 to 6 loose bowel movements daily. Which test would *not* be appropriate at this time?

a. CT enterography
b. Colonoscopy
c. C-reactive protein
d. Capsule endoscopy
e. Stool testing for *Clostridium difficile*

V.8. A 28-year-old man presents for evaluation of bloody diarrhea. He has had 4 to 6 loose, bloody bowel movements daily for the past 5 weeks. *Clostridium difficile* toxin assay is negative. Colonoscopy shows inflammation around the appendix and in the sigmoid colon and rectum, with normal mucosa in the terminal ileum, ascending colon, transverse colon, and descending colon. Biopsy specimens from the inflamed regions show mild chronic active colitis, and biopsy specimens from the areas in the colon that appeared normal are histologically normal. What is the most likely diagnosis?

a. Crohn colitis
b. Ischemic colitis
c. Ulcerative colitis
d. Microscopic colitis
e. Infectious colitis

V.9. A 27-year-old woman with a 4-year history of Crohn colitis stopped taking her medical therapy 8 months ago. She now presents with a 2-week history of perianal pain. One week ago, a "boil" developed adjacent to the anus. It was painful to touch and increased in size until it began draining cloudy fluid 2 days ago. She has noted air bubbles in her urine over the past month. Perianal examination shows 2 large perianal skin tags and dermatitis without any areas of fluctuance, tenderness, or obvious fistulous openings. Which test is best to evaluate these symptoms?

a. CT of the pelvis
b. MRI of the pelvis
c. CT enterography
d. Colonoscopy
e. Capsule endoscopy

V.10. A 25-year-old man with terminal ileal Crohn disease comes for advice on medical therapy. Since he received the diagnosis 2 years ago, he has been treated with prednisone, but whenever he decreases the dosage to less than 5 mg daily, he has abdominal pain, diarrhea, and arthralgias. The joint symptoms have been getting worse and are limiting his ability to work. In addition, he has been having problems with insomnia and acne, which he attributes to the prednisone. What is an appropriate therapeutic option for this patient?

a. Start azathioprine at 5 mg/kg daily after checking the TPMT level, and begin tapering the prednisone dose in 3 months
b. Start methotrexate at 25 mg subcutaneously weekly, and begin tapering the prednisone dose
c. Add a COX-2 inhibitor for joint pain
d. Start high-dose 5-ASA for steroid sparing
e. Add budesonide and taper the prednisone dose

V.11. A 28-year-old man with a history of steroid-dependent Crohn disease has been receiving infliximab therapy for 3 years. Over the past year, he has required dose escalation, and he is now receiving 10 mg/kg every 4 weeks. Six months ago, azathioprine was added at a dosage of 2.5 mg/kg daily. Despite this therapy, his symptoms return 3 weeks after receiving an infliximab infusion. His test results are positive for antibodies to hepatitis A virus, hepatitis B virus, and the JC polyomavirus. His PPD is negative. What is the best next step?

a. Increase the azathioprine dosage to 5 mg/kg daily after rechecking the TPMT level
b. Increase the infliximab dosage to 15 mg/kg every 4 weeks
c. Premedicate with methylprednisolone and diphenhydramine before each dose of infliximab
d. Change to another anti-TNF agent
e. Change to natalizumab

V.12. A 27-year-old man with a 2-year history of left-sided ulcerative colitis is hospitalized for a flare of disease. He has been receiving intravenous corticosteroids for 5 days without any

response. Surgical options have been discussed with him, but he does not wish to have surgery. What is the most appropriate therapeutic plan at this point?

a. Continue intravenous corticosteroid therapy for the next 5 days
b. Start methotrexate 25 mg subcutaneously every week
c. Start cyclosporine 5 mg/kg intravenous infusion
d. Start infliximab 5 mg/kg intravenously at weeks 0, 2, and 6
e. Start azathioprine 2.5 mg/kg daily by mouth

V.13. A 38-year-old man who is HLA-B27 positive and has chronic ulcerative colitis presents with a 6-month history of lower back pain. The pain is worse when he first awakens and improves throughout the day. On physical examination, spinal flexion is slightly limited. What treatment should you recommend?

a. Ibuprofen
b. Physical therapy
c. Colectomy
d. Hydrocodone
e. Tramadol

V.14. Osteoporosis is fairly common in patients with IBD. Which of the following is *not* a risk factor for osteoporosis?

a. Corticosteroids
b. Vitamin D deficiency
c. Increased physical activity
d. Active inflammation of the bowel
e. Calcium malabsorption

V.15. A 22-year-old man recently received a diagnosis of extensive ulcerative colitis. Colonoscopy at the time of diagnosis showed mildly active disease throughout the colon with no evidence of dysplasia or polypoid lesions. He began therapy with mesalamine 2.4 g daily. Routine blood work shows an elevated alkaline phosphatase level. He undergoes magnetic resonance cholangiopancreatography and is given a diagnosis of PSC. When should he undergo his next colonoscopy?

a. In 8 years
b. In 2 years
c. In 6 months
d. In 1 year
e. In 5 years

V.16. A 62-year-old woman with ileocolonic Crohn disease presents with worsening diarrhea, stools of oatmeal consistency, bloating, nausea, and weight loss. On physical examination, lower extremity edema is apparent. Laboratory test results are as follows: albumin 2.0 g/dL, AST 56 U/L, ALT 48 U/L, alkaline phosphatase 300 U/L, creatinine 2.6 mg/dL, and decreased gamma globulins. A colonoscopy is performed, and Congo red staining from rectal biopsies confirms the diagnosis. Extracellular tissue deposition of which of the following proteins is responsible for this patient's disease process?

a. Serum amyloid A protein
b. β_2-Microglobulin
c. Immunoglobulin light chain fragments
d. Myoglobin
e. Collagen

V.17. A 36-year-old woman has ileal Crohn disease. When an ulcer develops on her lower extremity with violaceous undermined borders, she is seen by a dermatologist who gives a diagnosis of pyoderma gangrenosum. Which of the following treatments should be *avoided*?

a. Surgical débridement
b. Infliximab
c. Topical tacrolimus
d. Anti–TNF-α agents
e. Corticosteroids

V.18. A 68-year-old man with ulcerative colitis presents with eye pain, redness of the eye, and headaches. Although he has received many courses of corticosteroids in the past, his colitis is currently in remission with azathioprine. He is HLA-B27 positive, and he has a history of sacroiliitis. He is referred to an ophthalmologist, who notes intense redness in the center of the eye which lessens peripherally. Which of the following is the correct diagnosis?

a. Scleritis
b. Glaucoma
c. Iritis
d. Episcleritis
e. Cataracts

V.19. A 51-year-old man presents with a 2-day history of bloody diarrhea, having experienced watery diarrhea for 2 days before the appearance of bloody stools. The patient has not received antibiotics recently. On examination, he is afebrile, with mild nonspecific abdominal tenderness and active bowel sounds. Laboratory studies reveal a normal serum WBC count, with a stool sample showing many fecal leukocytes. What is the most likely cause of symptoms?

a. *Clostridium difficile*
b. *Salmonella*
c. *Campylobacter*
d. *Shigella*
e. *Yersinia*

V.20. A 24-year-old man presents to the emergency department with watery diarrhea. His gastrointestinal tract symptoms had begun 48 hours earlier with nausea and vomiting. The patient had eaten at a Chinese restaurant. He has not had a fever, recent antibiotics, or infectious contacts. He has not started taking any new medications, and he has no significant medical history. What is the most likely cause of this patient's acute diarrhea?

a. *Staphylococcus aureus*
b. *Bacillus cereus*
c. *Clostridium perfringens*
d. *Listeria monocytogenes*
e. *Clostridium difficile*

V.21. A 74-year-old woman presents with a 2-week history of watery diarrhea. She reports passing 6 to 8 watery non-bloody stools daily. Approximately 6 weeks before the onset of diarrhea, she received a course of ciprofloxacin for a urinary tract infection. On clinical examination, the patient's vital signs are normal and she has mild nonspecific abdominal tenderness. Laboratory test results include a serum WBC count of 18,000/μL. Stool studies show the presence of many leukocytes. A stool sample is positive for *Clostridium difficile* toxin. What treatment would you recommend?

a. Loperamide, titrating to control symptoms
b. Fidaxomicin 200 mg twice daily for 10 days
c. Metronidazole 500 mg 3 times daily for 10 days
d. Vancomycin 125 mg 4 times daily for 10 days
e. Vancomycin 500 mg 4 times daily for 10 days

V.22. A 40-year-old man presents with a 1-week history of large-volume watery diarrhea. There has not been any blood. He reports significant mid-abdominal cramping and excessive gas. He was recently camping with his family. The family used only bottled water for consumption. The patient swam in rural lakes but did not swallow lake water. What is the most likely cause of this man's illness?

a. *Salmonella typhi*
b. *Cryptosporidium parvum*

c. *Campylobacter jejuni*
d. *Clostridium difficile*
e. *Giardia intestinalis*

V.23. A 40-year-old woman presents with a 5-day history of large-volume watery diarrhea. Her appetite is poor, and she reports significant nausea, bloating, flatulence, and cramping. She has not received antibiotics recently. She reports that she eats a diet rich in fresh fruits and has enjoyed large quantities of raspberries recently. Which of the following is most likely to help this patient?

a. Vancomycin
b. Trimethoprim-sulfamethoxazole
c. Tetracycline
d. Amoxicillin-sulbactam
e. Bismuth subsalicylate

V.24. A healthy 25-year-old man presents with a 3-day history of watery diarrhea. At the onset of symptoms, the patient also experienced vomiting that lasted for 12 hours. He has experienced muscle aches and fatigue. He was on a remote hunting and camping trip recently. He has 2 children in day care who have not been ill. Which of the following is the most likely diagnosis?

a. Giardiasis
b. Cryptosporidiosis
c. Viral gastroenteritis
d. Foodborne illness from *Staphylococcus aureus*
e. Yersiniosis

V.25. A 48-year-old woman with anemia is found to have an adenocarcinoma in the ascending colon. Her mother had uterine cancer diagnosed at age 72. Immunohistochemical staining for mismatch repair enzymes reveals deficient expression of MLH1; however, DNA sequencing does not reveal a mutation of the *MLH1* gene. The patient's tumor is also found to have a V600E *BRAF* mutation. Which of the following is most likely to be true?

a. The patient's tumor also contains mutant *KRAS*
b. The patient's tumor shows hypermethylation of the *MLH1* gene
c. The patient has hereditary nonpolyposis colon cancer (Lynch syndrome)
d. The patient's first-degree relatives should have *MLH1* gene sequencing
e. The patient's tumor should be tested for microsatellite instability

V.26. A 27-year-old woman with chronic diarrhea is found to have hundreds of polyps throughout her colon. Multiple polypectomy specimens show adenomatous histology. She has 2 healthy brothers and 3 healthy children aged 1, 3, and 7 years. Which of the following is most correct?

a. She should undergo intensive, annual colonoscopic surveillance for colon cancer
b. The likelihood that she inherited a mutant *APC* gene from 1 of her parents is greater than 95%
c. Her children should undergo genetic testing immediately
d. Her siblings should undergo prophylactic colectomy
e. If her *APC* gene testing is negative, her children should undergo endoscopy around age 10 to 12

V.27. An 18-year-old man presents with abdominal pain, constipation, and painless hematochezia. He undergoes diagnostic colonoscopy. A single hamartomatous polyp is found in the transverse colon. There is no family history of colon cancer. Which of the following should be done next?

a. Offer reassurance and symptom-directed management
b. Perform upper endoscopy and computed tomographic enteroclysis
c. Refer the patient for *SMAD4* gene testing
d. Offer colonoscopy to the patient's siblings, every 1 to 2 years, starting at age 15
e. Continue colonoscopy in this patient every 1 to 3 years until age 70

V.28. In the treatment of metastatic colorectal cancer, which of the following is true?

a. *KRAS* mutation status will affect the initial choice of cytotoxic chemotherapy
b. Patients with mutant *KRAS* should have panitumumab instead of cetuximab
c. Patients with mutant *KRAS* should not receive bevacizumab
d. All patients with liver metastases should be referred for palliative chemotherapy
e. Resection of the primary tumor may not be required

V.29. In which racial or ethnic group is colorectal cancer incidence and mortality highest?

a. White
b. African American
c. Asian American or Pacific Islander
d. American Indian or Alaskan Native
e. Hispanic or Latino

V.30. At screening colonoscopy, an otherwise healthy 50-year-old man is found to have 35 polyps, ranging in size from 2 to 13 mm. Representative polyp specimens have tubular adenomatous histology. He has no known family history of cancer. Which of the following is true?

a. With no family history, an *APC* mutation is unlikely
b. With no family history, a mutation in *MYH* is unlikely
c. If biallelic *MYH* mutation is confirmed, he will need upper endoscopy
d. If biallelic *MYH* mutation is confirmed, his children should be referred for genetic testing
e. The largest polyp should undergo mismatch repair enzyme testing

V.31. A 27-year-old woman presents with lifelong constipation. She describes infrequent defecation (once every 10 days), excessive straining at defecation, and difficulty in passing stools, with the need to digitate the rectum to facilitate stool passage. Although she has used various laxatives and her stools are soft, she still has difficulty defecating. She denies any sexual or emotional abuse. She has not had any pelvic surgery or vaginal deliveries. On rectal examination, the anal sphincter pressure is elevated and there is tenderness of the puborectalis muscle posteriorly with paradoxical contraction of the external anal sphincter and puborectalis muscle with simulated defecation. What is the best next step in the management of this patient?

a. Kegel exercises
b. Anorectal manometry with balloon expulsion
c. Subtotal colectomy with ileorectostomy
d. Lubiprostone 24 mcg twice daily
e. Linaclotide 145 mcg once daily

V.32. A 55-year-old woman presents for further evaluation of abdominal cramping pain and diarrhea. She reports a 2-year history of recurrent crampy lower abdominal pain associated with abdominal bloating and frequent watery stools. She denies fever, weight loss, anorexia, or bloody stools. Laboratory findings are normal for a complete blood cell count and iron studies. Colonoscopy 5 years earlier for colon cancer screening was normal. What would be the next appropriate test for evaluating this patient's symptoms?

a. Stool studies for ova and parasites
b. Colonoscopy with random biopsies

c. IgA and IgG antigliadin antibody testing
d. Glucose-hydrogen breath test
e. Thyrotropin level determination

V.33. A 35-year-old woman presents for evaluation of refractory constipation that began during adolescence. She has infrequent stools (1 every 2 weeks) when not using laxatives or enemas. She reports straining excessively, passing hard pebbly stools, and spending a long time on the toilet. She has tried various laxatives (milk of magnesia, polyethylene glycol, lactulose, bisacodyl, senna, lubiprostone, and linaclotide) with little success. She has mild intermittent abdominal bloating but denies abdominal pain. On physical examination she appears well. Her abdomen is soft and not distended, with active bowel sounds. Rectal examination shows normal anal sphincter tone without stool in the rectum and appropriate relaxation of the puborectalis muscle and external anal sphincter with simulated defecation. She has undergone an extensive evaluation, including a colonoscopy, which was difficult and showed a tortuous and redundant sigmoid colon. She had a meglumine diatrizoate (Gastrografin) enema; there was no dilated bowel. A Sitzmarks study showed prolonged transit. Anorectal manometry with balloon expulsion was normal. The patient is frustrated with her ongoing symptoms and lack of response to laxatives and is interested in surgery. Which of the following would be the surgery of choice for her condition?

a. Segmental sigmoid resection
b. Proctocolectomy with end ileostomy
c. Subtotal colectomy with ileorectostomy
d. Subtotal colectomy with ileoanal anastomosis
e. Rectopexy

V.34. A 22-year-old woman presents with a 2-year history of recurrent crampy lower abdominal pain associated with abdominal bloating and frequent loose stools. She denies fever, weight loss, anorexia, or bloody stools. Physical examination findings are normal. Laboratory testing shows a normal complete blood cell count and C-reactive protein level. Which of the following tests should be performed?

a. Abdominal ultrasonography
b. Glucose-hydrogen breath test
c. Stool ova and parasite examination
d. Thyrotropin level determination
e. IgA tissue transglutaminase antibody testing

V.35. Linaclotide is an FDA-approved treatment for idiopathic chronic constipation and IBS-C. What is the mechanism by which linaclotide improves symptoms of constipation?

a. GC-C agonist
b. Chloride channel activator
c. Serotonin 4 receptor agonist
d. Serotonin 3 receptor antagonist
e. Motilin agonist

V.36. Approximately 10% of patients with IBS have symptom onset after an episode of infectious enteritis. Which of the following is the strongest risk factor for PI-IBS?

a. Prolonged duration of initial illness
b. Depression
c. Female sex
d. Use of antibiotics
e. Age older than 60 years

V.37. A 45-year-old woman presents with a 5-year history of constipation. She has a bowel movement every 3 days, strains to defecate even soft stools, complains of a sense of anorectal blockage during defecation, and is not satisfied thereafter. She also has abdominal bloating and sometimes sees blood on the toilet paper. A flexible sigmoidoscopy is negative. She has tried laxatives, but they work only if her stools are loose. What is the best next step?

a. Reassurance alone
b. Anorectal manometry and rectal balloon expulsion test
c. Pelvic floor retraining
d. Colectomy
e. Psychiatric consultation

V.38. Which of the following statements regarding colonic and anorectal tests in chronic constipation is accurate?

a. The rectal balloon expulsion test is not useful for identifying defecatory disorders
b. Patients with chronic constipation and slow colonic transit have slow-transit constipation
c. False-positive results can occur with anorectal tests
d. The results of anorectal manometry, rectal balloon expulsion test, and defecography are always in agreement
e. The rectoanal gradient during simulated evacuation is always positive in asymptomatic people

V.39. A 25-year-old woman has had constipation for 2 years. She passes hard stools approximately twice weekly and has abdominal bloating but no symptoms suggestive of pelvic floor dysfunction. She denies alarm symptoms or a family history of colon cancer. Her symptoms have not responded to dietary fiber supplementation. A careful digital rectal examination reveals normal anal tone at rest, normal puborectalis and anal sphincter contraction during voluntary effort, and normal perineal descent during simulated evacuation. What is the best next step?

a. Colonoscopy
b. Lubiprostone
c. Osmotic or stimulant laxatives (or both)
d. Colonic transit study
e. Anorectal manometry

V.40. Which of the following statements regarding management of fecal incontinence is most accurate?

a. Surgical repair of anal sphincter defects is an effective long-term solution for patients with fecal incontinence and anal sphincter defects
b. Pelvic floor retraining by electromyographically assisted biofeedback therapy is superior to Kegel exercises
c. Sacral nerve stimulation should be considered for patients with significant symptoms that have not improved with medical therapy
d. Management of bowel disturbances is not useful
e. Artificial anal sphincter and dynamic graciloplasty have low morbidity

V.41. A 65-year-old woman has had diarrhea and fecal incontinence since she had a cholecystectomy 3 years ago. She has 3 semiformed bowel movements daily, which are preceded by lower abdominal discomfort and urgency. She is incontinent for a small amount of semiformed stool twice weekly. She wears a panty liner. There is no history of gastrointestinal bleeding, weight loss, or other alarm symptoms. Her past medical history is notable for 3 vaginal deliveries with grade 3 perineal injury during 1 delivery. Digital rectal examination findings include normal anal resting tone, a decreased puborectalis "lift" to voluntary command, an anterior sphincter defect, and normal perineal descent during simulated evacuation. Colonoscopy results were normal 5 years ago. Which of the following is the best next step?

a. Colonoscopy with random colonic biopsies
b. Anorectal manometry
c. Endoanal ultrasonography

d. Routine laboratory testing
e. Empirical treatment with a bile acid–binding resin

V.42. Which of the following statements about anorectal diagnostic tests is most accurate?

a. Anal pressures should be compared with normal values obtained with the same technique in age- and sex-matched asymptomatic people
b. PNTML accurately identifies pudendal neuropathy
c. All patients with fecal incontinence require anorectal testing
d. Anal resting and squeeze pressures are reduced in all patients with fecal incontinence
e. Anal resting and squeeze function cannot be accurately evaluated by digital rectal examination

V.43. A 28-year-old woman who is 28 weeks pregnant presents to the emergency department with a 1-day history of black, tarry stools and 3 episodes of hematemesis. She has no significant past history and saw her obstetrician 2 weeks ago for a routine follow-up visit. Her hemoglobin was 13.2 g/dL at that time. Currently, she is tachycardic (heart rate, 130 beats per minute) and her hemoglobin is 10.1 g/dL. Her INR and platelet count are normal. You are the on-call gastroenterologist. What should you recommend now?

a. Start an oral PPI twice daily with outpatient obstetric follow-up in the morning
b. Admit to the obstetric service for observation
c. Start ranitidine orally twice daily
d. Arrange for propofol anesthesia and upper endoscopy now

V.44. A 23-year-old woman is in her first trimester of pregnancy. She is complaining of significant nausea (but no vomiting) that is persistent throughout the day. She can keep down fluids and food but has difficulty concentrating at work. What is the best choice for therapy?

a. Intravenous fluids and parenteral nutrition
b. A domperidone prescription that she can send to Canada
c. Rectal promethazine
d. PPI therapy
e. Pyridoxine

V.45. A 30-year-old woman who is in the early part of the third trimester of pregnancy is complaining of worsening heartburn. She describes a burning sensation in her chest after meals which is particularly worse at night. She does not have any dysphagia or regurgitation. Her pregnancy is otherwise progressing normally. She is complaining, however, that her heartburn is requiring her to sleep in a recliner chair in the living room rather than in her bed and is asking for advice. What should you advise?

a. Reassurance alone
b. Begin PPI therapy
c. Upper endoscopy to rule out erosive esophagitis
d. Begin sodium bicarbonate solution

V.46. A 28-year-old woman who just found out that she is 9 weeks pregnant has a history of Crohn disease of the terminal ileum in remission on azathioprine. She has had aggressive disease in the past and has had 2 ileal resections. She is concerned because azathioprine is a category D medication, but she thinks she remembers you telling her that for IBD there are data that suggest that continued use of azathioprine carries a low risk. She is currently feeling well and is excited about the prospect of being a mother. What should you advise her at this time?

a. Continue azathioprine
b. Stop azathioprine
c. Stop azathioprine and start mesalamine
d. Stop azathioprine and start a biological agent
e. Stop azathioprine and start low-dose prednisone

V.47. A 29-year-old woman with known autoimmune hepatitis after a liver transplant 2 years ago is referred to you by her obstetrician for treatment recommendations since she is now 10 weeks pregnant. She received a cadaveric organ 2 years ago for fulminant autoimmune hepatitis and has done very well with only a mild case of rejection 6 months after the transplant which was treated with high-dose steroids. Her current antirejection regimen is tacrolimus twice daily (most recent level, 6 ng/mL). Current laboratory test results include the following: AST 35 U/L, ALT 32 U/L, total bilirubin 0.9 mg/dL, alkaline phosphatase 40 U/L, and albumin 4.1 g/dL. What should you counsel your patient to do at this point?

a. Double the current dose of tacrolimus
b. Stop tacrolimus and switch to mycophenolate mofetil
c. Continue the current dose of tacrolimus
d. Consider termination of the pregnancy
e. Receive pulsed high-dose steroids

V.48. A 30-year-old woman with no significant past medical history is referred by her obstetrician for the complaint of constipation. The patient is currently 24 weeks pregnant and notes that she is having very infrequent stools (1 every 3 days), with discomfort and bloating. Before her pregnancy, she had 1 formed stool daily. She is not losing any weight and her fetus is an appropriate size for the gestational age. She is not having any nausea or vomiting and has a good appetite. She says she tries to eat at least 2 pieces of fresh fruit daily and has wheat toast for breakfast. She has no problems with urination. She has not seen any blood in her stool. Recent fasting blood glucose and sensitive thyrotropin levels were normal. There is no family history of colon cancer. What should you recommend?

a. Colonoscopy
b. Flexible sigmoidoscopy
c. Increased supplemental fiber intake
d. Castor oil
e. Magnesium citrate

Answers

V.1. Answer e.

This question highlights the broad differential diagnosis for a young patient presenting with abdominal pain and diarrhea. Concerning features include the chronicity of symptoms, weight loss, nocturnal symptoms, and the passage of blood. This patient requires additional assessment to exclude underlying IBD or an infection. One should not forget about the possibility of pregnancy in any young female patient presenting with abdominal pain, since certain tests, such as CT, should be avoided. Antidiarrheal agents, such as loperamide, are generally avoided in patients with new-onset bloody diarrhea.

V.2. Answer d.

The true statement is that penetrating perianal and intra-abdominal disease can develop in Crohn disease patients. These patients are at increased risk of colon cancer and should undergo surveillance colonoscopies after 8 to 10 years of disease if more than one-third of the colon is involved. Noncaseating granulomas are a histologic feature of Crohn disease. Serology with ASCA and ANCA testing can be beneficial in some cases, but it is not required to make a diagnosis of IBD. Young age at diagnosis is consistent with Crohn disease.

V.3. Answer c.
The incidence of *Clostridium difficile* infections has dramatically increased in the population and in IBD patients. These infections can occur in IBD outpatients even without antibiotic exposure. IBD-directed therapy should not be adjusted until infection is excluded and objective evidence of active IBD is obtained. CT enterography is excellent for small-bowel Crohn disease assessments but less than optimal for colonic interrogations without a rectal contrast agent. Colonoscopy certainly may be needed for this patient, but typically *C difficile* should be excluded as a first step.

V.4. Answer e.
CT enterography and MR enterography have become powerful tools for diagnosing IBD. They provide objective transmural disease assessments and are used to detect penetrating disease and to diagnose extraintestinal disease manifestations. A large prospective study with IBD patients showed that CT enterography alters management plans for up to 50% of patients.

V.5. Answer c.
A woman in remission before pregnancy is more likely to remain in remission during pregnancy. Use of methotrexate is contraindicated during pregnancy and should be discontinued at least 3 months before conception. Fertility is normal in patients with inactive IBD who have not had abdominal or pelvic operations. Pregnancy is not contraindicated in patients with an ileostomy. Flares are most common in the first trimester and the postpartum period.

V.6. Answer d.
IBD patients have no specific dietary restrictions. The exception might be a patient with small-bowel strictures, for which a low-residue diet is often recommended. Lactose intolerance is more common among Crohn disease patients. Women have a higher overall incidence of Crohn disease. Ulcerative colitis is historically more common than Crohn disease. IBD is more common among Ashkenazi Jews. Ulcerative colitis is more common among nonsmokers.

V.7. Answer d.
This patient is having symptoms of active Crohn disease. However, the symptoms are nonspecific, and, therefore, further investigation is warranted to determine whether her disease is flaring. For this purpose, CT enterography, colonoscopy, and C-reactive protein would all be reasonable. In addition, *Clostridium difficile* is a common cause of symptomatic flares in patients with IBD, and testing the stool for this infection would also be appropriate. However, given the nausea and vomiting, obstruction should be ruled out before pursuing a capsule endoscopy since the risk of capsule retention would be increased in a patient with obstruction.

V.8. Answer c.
Although this patient has discontinuous inflammation, raising the possibility of Crohn colitis, the presence of an "appendiceal patch" is now recognized as part of the clinical picture of ulcerative colitis and, by itself, does not warrant a diagnosis of Crohn disease, particularly with a normal-appearing terminal ileum. Ischemic colitis and microscopic colitis would be unusual in a 28-year-old, and furthermore, the histologic findings on colon biopsies are consistent with IBD and not ischemic colitis, microscopic colitis, or infectious colitis.

V.9. Answer b.
In this patient with established Crohn disease, the presence of perianal pain and a "boil" suggest the development of a perianal fistula or abscess (or both). Furthermore, the presence of air bubbles in her urine is worrisome for an enterovesical fistula. CT enterography and dedicated CT of the pelvis are relatively insensitive for perianal disease, given the bony artifacts that are often present. Colonoscopy would be useful to assess the status of mucosal inflammation but would not be a useful test for characterizing perianal disease. Similarly, capsule endoscopy might be useful to evaluate small-bowel mucosal inflammation, but it would provide no useful information with regard to perianal anatomy.

V.10. Answer b.
This young man has steroid-dependent ileal Crohn disease and needs a steroid-sparing maintenance medication. There is no evidence for a maintenance effect for budesonide or for 5-ASA drugs. Both azathioprine and methotrexate are effective for maintenance therapy, but the dose listed for azathioprine is much higher than the recommended dose (2.0-2.5 mg/kg daily). His joint symptoms are likely related to Crohn disease and should respond with appropriate treatment of the bowel inflammation. In that case, COX-2 inhibitors would likely not be necessary, and long-term use of NSAIDs, even COX-2 selective agents, might increase the risk of a flare of Crohn disease. Furthermore, methotrexate is known to have effects on arthritis and would, therefore, be a particularly attractive option for therapy in this case.

V.11. Answer d.
This patient's long-standing Crohn disease has been maintained with infliximab, but he has required progressive dose escalation. Despite this, as well as the addition of an appropriate dose of azathioprine, he is still having breakthrough symptoms before his next infliximab dose. He is already receiving a large dosage of infliximab, and adding additional infliximab would be increasingly costly and unlikely to provide much benefit. His azathioprine dosage is appropriate, and increasing it further, particularly to 5 mg/kg daily, would carry a high risk of bone marrow toxicity. Premedicating with methylprednisolone and diphenhydramine before infliximab dosing may decrease the likelihood that antibodies to infliximab will develop, but in this case, the patient almost certainly has antibodies to infliximab and the benefit of these medications now is unclear at best. Therefore, the options to be considered would be switching to another anti-TNF agent or switching to a different class of medications with natalizumab. Unfortunately, his test results are positive for antibodies to JC polyomavirus, and he would have an unacceptably high risk of progressive multifocal leukoencephalopathy; therefore, he should not receive natalizumab.

V.12. Answer d.
This patient with a flare of ulcerative colitis has not responded to 5 days of intravenous corticosteroids. Further treatment with intravenous corticosteroids alone is not likely to achieve remission and would predispose to steroid-related side effects and other complications. Methotrexate is not well studied in ulcerative colitis and so is not a recommended treatment. Azathioprine does have some weak evidence for a steroid-sparing maintenance effect in ulcerative colitis, but the onset of action is too slow to be used in steroid-refractory cases such as this. Therefore, the options to consider are surgical therapy or medical therapy with either anti-TNF or cyclosporine. The recommended dose

of cyclosporine is 2 to 4 mg/kg; therefore, the best choice here would be infliximab.

V.13. Answer b.
This patient has inflammatory back pain and is positive for HLA-B27. His history and physical examination findings are highly suggestive of ankylosing spondylitis. The first-line therapy for ankylosing spondylitis is referral for physical therapy.

V.14. Answer c.
Osteoporosis is present in 15% of patients with IBD. Risk factors for osteoporosis in this patient population include frequent corticosteroid use or corticosteroid use for 3 or more months, vitamin D deficiency, calcium and magnesium malabsorption, and inflammation leading to increased cytokine release contributing to bone resorption. Decreased physical activity is also a risk factor for osteoporosis. Patients with risk factors for osteoporosis should undergo screening with a DEXA scan.

V.15. Answer d.
Although this patient has a recent diagnosis of ulcerative colitis, he also has PSC. The diagnosis of PSC significantly increases his risk of colorectal cancer. All patients with IBD and PSC should undergo annual surveillance colonoscopy beginning at the time of the PSC diagnosis.

V.16. Answer a.
This is secondary (reactive) amyloidosis. Secondary amyloidosis occurs with chronic inflammatory disease (eg, IBD, rheumatoid arthritis, chronic infection, familial Mediterranean fever). Secondary amyloidosis can affect any organ, although the kidneys are most commonly involved. Gastrointestinal tract involvement is more common in secondary amyloidosis than in primary amyloidosis. AA amyloid fibrils are derived from serum amyloid A protein, an acute phase reactant. Fibril deposition in the gastrointestinal tract mucosa or neuromuscular fibers (or both) can lead to dysmotility, bacterial overgrowth, and malabsorption.

V.17. Answer a.
Pyoderma gangrenosum can be very challenging to treat. This skin condition may or may not parallel bowel inflammation. First-line therapy is usually corticosteroids, although topical tacrolimus is sometimes helpful. Other therapies, including cyclosporine, tacrolimus, azathioprine, and anti–TNF-α agents, have been used to treat pyoderma gangrenosum. Pyoderma gangrenosum is a pathergic condition; therefore, any trauma (including surgical débridement) to the lesion could worsen the lesion.

V.18. Answer c.
This patient's history of corticosteroid use increases his risk of cataracts or glaucoma. However, his current presentation does not suggest either of these diagnoses. Both scleritis and episcleritis parallel disease activity, whereas iritis may or may not parallel disease activity. Iritis is often associated with other extraintestinal manifestations, and up to 50% of patients with acute iritis are HLA-B27 positive. The characteristic finding on examination is a ciliary flush (intense redness in the center of the eye which lessens in intensity peripherally).

V.19. Answer c.
The patient has presented with an acute biphasic diarrheal illness: initially watery diarrhea and subsequently bloody diarrhea. There are many fecal leukocytes on stool analysis. Such a biphasic presentation may be seen with *Campylobacter* and *Shigella* infections. *Campylobacter* is more common than *Shigella*, especially in patients without risk factors for *Shigella* infection, such as daycare exposure. Diarrhea associated with *Yersinia* and *Clostridium difficile* is usually nonbloody, and *Salmonella* typically does not cause a biphasic illness.

V.20. Answer b.
In a case of suspected food poisoning, if nausea and vomiting are the predominant initial symptoms, the most likely cause would be *Staphylococcus aureus, Bacillus cereus*, or *Clostridium perfringens*. In this particular case, the prior ingestion of Chinese food makes *B cereus* the most likely cause of this patient's symptoms. *Listeria monocytogenes* may cause an acute gastroenteritis following ingestion of foods such as soft cheese and lunch meats. *Listeria* is of particular concern in immunocompromised hosts and pregnant women. *Clostridium difficile* is unlikely in the absence of recent antibiotic use.

V.21. Answer d.
Initial therapy for *Clostridium difficile* infection is based on the severity of clinical presentation. In patients with mild disease (WBC count <15,000/μL, creatinine <1.5 times baseline), first-line therapy is metronidazole 500 mg 3 times daily for 10 days. In patients with severe disease (WBC count >15,000/μL, creatinine >1.5 times baseline), first-line therapy is vancomycin 125 mg 4 times daily for 10 days. A higher dose of vancomycin would not provide additional benefit. Antidiarrheals should generally be avoided in patients with infectious diarrhea. Fidaxomicin may be considered for patients with multiple recurrences of *C difficile* infection.

V.22. Answer e.
The history of large-volume watery diarrhea associated with cramping abdominal pain and excess gas suggests a small-bowel location. Of the listed potential causes, these symptoms are more likely related to either *Giardia* or *Cryptosporidium*, both of which may be acquired by ingestion of contaminated water. *Giardia* is more common and may result from ingestion of small volumes of contaminated water. *Cryptosporidium* is less common and more likely in immunocompromised hosts.

V.23. Answer b.
The patient presents with acute-onset, large-volume watery diarrhea associated with bloating and cramping. The clinical presentation suggests a small-bowel pathogen. Given the recent ingestion of raspberries, the most likely diagnosis is *Cyclospora* infection. This condition is best treated with a 7-day course of trimethoprim-sulfamethoxazole.

V.24. Answer c.
The most common cause of acute-onset vomiting and diarrhea is viral gastroenteritis. The clinical presentation is not suggestive of a small-bowel source of diarrhea. There was no reported potential source of foodborne toxin (*Staphylococcus aureus*).

V.25. Answer b.
Mutations in *BRAF* and *KRAS* are considered mutually exclusive events in colon cancer tumorigenesis. *BRAF* mutations are strongly associated with methylation of the *MLH1* promotor, causing noninherited gene silencing. Because the patient's tumor contains mutant *BRAF* and no mutation of *MLH1* has been identified, she does not meet the diagnostic criteria for Lynch syndrome and relatives should not be offered testing. Microsatellite instability testing can be used to screen for tumors that are likely to show deficient mismatch repair enzyme expression, but it is not indicated after mismatch repair has been performed.

V.26. Answer e.
The patient presents with the classic phenotype of familial adenomatous polyposis, and colon cancer will inevitably develop at a young age. There is no role for surveillance, and colectomy is indicated. The patient should receive genetic counseling to determine whether she has a mutation in the *APC* gene; however, about 20% of patients with the classic FAP phenotype do not have a conclusive *APC* mutation. In another 25% of FAP probands, a de novo *APC* mutation will develop, and there are no affected ancestors. Siblings and children of those with *APC* mutations should also be offered genetic testing. At-risk relatives of probands with inconclusive gene testing should be offered endoscopic testing to confirm polyposis before colectomy. Children of affected individuals do not need genetic testing or endoscopy before age 10.

V.27. Answer a.
Sporadic juvenile hamartomatous polyps are common and occur in 1% to 2% of children; cancer risk is not increased. Reassurance and symptom-directed management should be offered. Juvenile polyposis is often defined as more than 10 polyps and is rare when occurring in a familial pattern (<1 per 100,000). Individuals with polyposis should be referred for genetic testing to identify germline mutations in *SMAD4, BMPR1A*, and *ENG*, all members of the transforming growth factor β pathway. Colon cancer risk is approximately 20% with a median age at onset of 37. Surveillance for dysplastic polyps is recommended for at-risk relatives and probands from age 15 to 70 in both the upper and lower gastrointestinal tract. This may be discontinued at age 40 for relatives of a proband without a confirmed gene mutation.

V.28. Answer e.
There are no prospectively validated molecular markers to guide clinicians in the initial choice of cytotoxic chemotherapy for palliation of metastatic colorectal cancer. Patients with mutant *KRAS* are less likely to benefit from EGFR inhibitors (cetuximab or panitumumab); *KRAS* status does not affect the outcomes for patients receiving bevacizumab, which impedes tumor angiogenesis via the VEGF pathway. Patients with isolated liver or lung metastases are potentially curable and should be referred to a surgeon. For asymptomatic patients with surgically incurable colorectal cancer, resection of the primary tumor is indicated only for patients with bleeding or impending obstruction.

V.29. Answer b.
According to data from the SEER program (2004-2008), cancer incidence and mortality have decreased for all ethnic groups except American Indian or Alaskan Native. However, African Americans still have the highest rates of new colorectal cancer diagnoses and deaths. Although some of the differences in survival are explained by stage at diagnosis, within-stage comparisons still show worse outcomes. These observations have led the American College of Gastroenterology and American Society for Gastrointestinal Endoscopy to recommend colorectal cancer screening for African Americans starting at age 45.

V.30. Answer c.
A patient who presents with polyposis (10-100 adenomas) in the absence of a family history should be evaluated for attenuated familial adenomatous polyposis or *MYH*-associated polyposis. Although *APC* mutations are inherited in an autosomal dominant manner, 25% occur de novo. *MYH*-associated polyposis is inherited in an autosomal recessive manner, requiring 2 mutant alleles. These patients are also at risk for gastric and duodenal polyps and should have upper endoscopy with a side-viewing examination. Monoallelic carriers (1%-2% of the population) may have a slight increase in colorectal cancer risk, but there is insufficient evidence to recommend heightened surveillance. To determine the risk of biallelic mutations in the patient's children, their mother should be tested for *MYH* carriage first. This patient does not meet Amsterdam criteria for Lynch syndrome and does not require mismatch repair testing; additionally, mismatch repair expression testing is carried out on cancers, not polyps.

V.31. Answer b.
This patient's history and physical examination findings are consistent with dyssynergic defecation (pelvic floor dysfunction). The most appropriate next step is to confirm the diagnosis by anorectal manometry with balloon expulsion. The cornerstone of therapy for dyssynergic defecation is pelvic floor retraining with biofeedback therapy. A subtotal colectomy with ileorectostomy is indicated for patients with medically refractory slow-transit constipation. Kegel exercises may be helpful for fecal incontinence, not dyssynergic defecation. Lubiprostone and linaclotide are indicated for IBS-C and functional constipation.

V.32. Answer b.
This patient's presentation is compatible with D-IBS. Several conditions mimic D-IBS, including celiac disease, small intestinal bacterial overgrowth, lactose maldigestion, and microscopic colitis. Routine diagnostic testing with complete blood cell count, serum chemistry testing, thyroid tests, stool studies, and abdominal imaging is not recommended for patients with typical IBS symptoms and no alarm features. It is recommended that serologic screening with IgA tissue transglutaminase antibody be performed for celiac disease in patients with D-IBS. IgA and IgG antigliadin antibodies lack sensitivity and specificity for celiac disease and are no longer recommended in the evaluation of celiac disease. A glucose-hydrogen breath test can be used to assess for small intestinal bacterial overgrowth; however, there are insufficient data to recommend testing for small intestinal bacterial overgrowth in IBS patients. Microscopic colitis is a common mimic of D-IBS, and the patient in this clinical scenario fits the demographic criteria for microscopic colitis (woman older than 50), so the best test would be colonoscopy with biopsies to evaluate for microscopic colitis.

V.33. Answer c.
This patient has medically refractory slow-transit constipation, for which a subtotal colectomy with ileorectal anastomosis (also referred to as an ileorectostomy) is the surgical procedure of choice. Patient selection is important to improve outcomes, and before proceeding with subtotal colectomy, it is important to exclude dyssynergic defecation, whole gut motility problems, and severe psychologic comorbidity. A segmental colonic resection, such as the sigmoid, is usually not successful because the abnormality with slow-transit constipation typically involves the entire colon. Ileostomy is an alternative surgical procedure for refractory slow-transit constipation; however, it is generally a less satisfactory option. A subtotal colectomy with ileoanal anastomosis is a technically challenging procedure that is not indicated unless megarectum is present. Rectopexy is a surgical option for patients with rectal prolapse.

V.34. Answer e.
This patient meets the Rome criteria for D-IBS and has no warning symptoms or signs. The consensus approach to a patient younger than 50 years who has symptoms compatible with D-IBS

is to screen for celiac disease with IgA tissue transglutaminase antibody testing. Other diagnostic tests in this clinical setting would not have a significantly higher yield than in the general population and are not indicated. It is important to recognize that IBS is a symptom-based diagnosis and that investigations should be limited. Guidelines recommend routine screening for celiac disease in patients with D-IBS (based on studies showing a 4-fold higher prevalence of biopsy-proven celiac disease in patients with IBS). However, the findings from a recent US multicenter trial, in which the prevalence of celiac disease in patients with IBS was similar to that for controls, challenge this recommendation.

V.35. Answer a.
Linaclotide is a GC-C agonist. Linaclotide binds to GC-C on the luminal surface of intestinal epithelium, which activates GC-C and increases intracellular and extracellular levels of cGMP. Elevated intracellular cGMP stimulates the secretion of chloride and bicarbonate into the intestinal lumen, causing an increase in intestinal fluid and faster transit. Lubiprostone is a chloride channel activator that acts locally on the apical membrane of the gastrointestinal tract to increase intestinal fluid secretion and improve fecal transit. Tegaserod is a serotonin 4 receptor partial agonist. Activation of serotonin 4 receptors increases the peristaltic reflex. Owing to its adverse cardiovascular effects, tegaserod was removed from the market. Alosetron is a selective antagonist of serotonin 3 receptors and is approved for treatment of constipation-predominant IBS. Motilin agonists include erythromycin and azithromycin, which augment gastric emptying.

V.36. Answer a.
Many risk factors for PI-IBS have been identified, including prolonged duration of initial illness, toxicity of infecting bacterial strain, smoking, female sex, depression, hypochondriasis, and treatment with antibiotics. Several studies have evaluated risk levels associated with predisposition to PI-IBS. Of the risk factors listed, prolonged duration of initial illness has the highest relative risk. Age older than 60 years may protect against PI-IBS.

V.37. Answer b.
The clinical features suggest pelvic floor dysfunction. While symptoms and a careful digital rectal examination may suggest a defecatory disorder, the diagnosis should be confirmed by anorectal manometry and a rectal balloon expulsion test. Pelvic floor retraining with biofeedback therapy is superior to laxatives for managing constipation due to a defecatory disorder.

V.38. Answer c.
Since anorectal tests may cause embarrassment, false-positive results may occur, even in asymptomatic people. Indeed, the rectoanal gradient during simulated evacuation is often negative (ie, rectal pressure is less than anal pressure) in asymptomatic people. Hence, tests need to be interpreted in the overall clinical context rather than in isolation. IBS-C is defined by symptoms; patients may have normal or delayed colonic transit. *Normal-transit constipation* is not synonymous with *IBS-C*. Up to 50% of patients with defecatory disorders have slow colonic transit. Therefore, it is necessary to exclude a defecatory disorder before concluding that patients with chronic constipation and slow colonic transit have slow-transit constipation. The results of anorectal manometry, rectal balloon expulsion test, and defecography often disagree.

V.39. Answer c.
Over-the-counter laxatives are effective and safe; hence, they are the first choice for young patients with constipation without alarm symptoms. In the absence of alarm symptoms, a colonoscopy and assessments of colonic transit and anorectal functions are not required initially. Likewise, newer agents, which are more expensive, should be reserved for patients in whom symptoms do not respond to therapy with first-line agents.

V.40. Answer c.
Several predominantly uncontrolled studies have suggested that sacral nerve stimulation may improve fecal continence. Sacral nerve stimulation is now approved for treating urinary and fecal incontinence. Continence improves in 80% to 90% of patients shortly after repair of anal sphincter defects but deteriorates over time thereafter; less than 20% of patients are continent at 5 years after the operation. Pelvic floor retraining by biofeedback therapy is not superior to Kegel exercises in patients who do not respond to measures to regulate bowel disturbances. Artificial anal sphincter and dynamic graciloplasty are associated with considerable morbidity, particularly wound infections, and are used sparingly in the United States.

V.41. Answer e.
In the absence of alarm symptoms, laboratory tests and colonoscopy are unnecessary, particularly since her symptoms began after a cholecystectomy; a bile acid–binding resin may be helpful. Likewise, anorectal manometry is indicated only if treatment of diarrhea does not improve the bowel symptoms. Endoanal ultrasonography would also be premature at this stage.

V.42. Answer a.
Because anal pressures decrease with age and are lower in women than in men, pressures should be compared with normal values obtained with the same technique in age- and sex-matched asymptomatic people. Anorectal testing is indicated for fecal incontinence when symptoms do not respond to management of bowel disturbances or local anorectal conditions. Anal resting and squeeze function can be accurately evaluated by a digital rectal examination; many patients with fecal incontinence pressures have normal anal resting and squeeze pressures. PNTML is not accurate for identifying pudendal neuropathy.

V.43. Answer d.
This pregnant patient is showing signs and symptoms of active gastrointestinal bleeding. She has an appropriate indication for endoscopy and should undergo endoscopy the same as a nonpregnant patient would in this clinical situation. She has evidence of blood loss and is tachycardic. Once the source of her bleeding is found, decisions about admission or dismissal can be made.

V.44. Answer e.
This pregnant patient is having nausea that is typical in the first trimester of pregnancy. She is not at risk for volume depletion but is symptomatic. Pyridoxine (vitamin B_6) is a category A medication for nausea induced by pregnancy and is the first-line choice for treatment. She does not fit the criteria for hyperemesis gravidarum or require hospitalization. Domperidone is not approved for use in the United States. Promethazine is second-line therapy, and PPI therapy is used for heartburn symptoms, not nausea.

V.45. Answer b.
Heartburn is a common symptom in pregnancy and is more common in the third trimester, but patients do not have to suffer with symptoms and can be treated. There is no indication for upper endoscopy at this point since she does not have any alarm

symptoms and has not received any treatment yet. Sodium bicarbonate can cause milk alkali syndrome and electrolyte imbalance in the fetus and is not recommended. Most of the PPIs are category B medications and are appropriate therapy for a symptomatic pregnant patient.

V.46. Answer a.
Azathioprine was given its category D rating in the mid 1950s when it was approved to treat leukemia. Data from populations as well as IBD centers suggest that the risk of an adverse birth event may actually be lower for women who continue to use a thiopurine since it controls active disease. In addition, by the time this patient learned that she was pregnant, organogenesis had already occurred, so that if she stopped taking the drug, she would only be putting her own health at risk. With her history of aggressive disease, monitoring alone, without use of medications, would set her up for problems if the disease flares. Mesalamine, while safe, is not appropriate treatment of Crohn disease in a patient such as this. Her disease is currently in remission, so starting a biological agent is not appropriate, nor is prescribing low-dose prednisone.

V.47. Answer c.
Her current laboratory tests suggest that she has good graft function, and her tacrolimus level is in the therapeutic range (3-7 ng/mL). Tacrolimus is a category C medication and is the preferred antirejection therapy when a graft is stable. There is no reason to recommend termination of the pregnancy since the patient's clinical course has been favorable. In addition, there is no indication for high-dose steroids right now since her rejection episode was in the past.

V.48. Answer c.
This patient has functional constipation, which is common during pregnancy. She has no alarm signs or symptoms to warrant endoscopy—constipation alone is not an indication for colonoscopy in a pregnant patient. Fiber therapy is the first-line treatment for pregnancy-induced constipation. Increasing dietary sources can be difficult, and thus, addition of a supplement is generally required. Castor oil is a category X therapy and should be avoided as it has been associated with uterine rupture. Magnesium citrate is low risk but only for occasional use; if the patient requires daily laxatives, docusate would be preferred.

VI

Liver

22

Approach to the Patient With Abnormal Liver Test Results and Acute Liver Failure[a]

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This chapter includes the following topics:

1. General discussion of commonly used liver tests
2. Differential diagnosis and discussion of diseases characterized by an increase in hepatocellular enzyme levels
3. Differential diagnosis and discussion of diseases characterized by an increase in cholestatic enzyme levels
4. Evaluation of patients who have jaundice
5. General approach for evaluating patients who have abnormal liver test results
6. Liver biopsy and other methods to assess fibrosis
7. Discussion of acute liver failure

Commonly Used Liver Tests

Aminotransferases (Alanine and Aspartate Aminotransferases)

The aminotransferases (also referred to as *transaminases*) are located in hepatocytes, and elevated serum levels are an indication of hepatocellular disease. Injury of the hepatocyte membrane allows these enzymes to "leak" out of hepatocytes, and within a few hours after liver injury, the serum levels of the enzymes increase. Aminotransferases consist of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). ALT elevation is more specific for liver injury than is AST elevation, although severe muscle injury may result in serum elevations of both enzymes. ALT has a longer half-life than AST; thus, improvements in ALT levels lag behind those of AST. Patients with liver disease and renal failure typically have lower levels of aminotransferases than those who have liver disease and normal renal function.

Alkaline Phosphatase

Alkaline phosphatase is an enzyme located on the hepatocyte membrane bordering the bile canaliculus. Because alkaline phosphatase is found also in bone and placenta, an increase in its level without other indication of liver disease should prompt further testing to discover whether the increase is from liver or from other tissues. One way of doing this is to determine the concentration of alkaline phosphatase isoenzymes. Another way is to determine the level of γ-glutamyltransferase, an enzyme of intrahepatic biliary canaliculi. Other than to confirm the liver origin of an increased level of alkaline phosphatase, γ-glutamyltransferase is of little use in the evaluation of diseases of the liver because its synthesis can be induced by many medications, thus decreasing its specificity for clinically important liver disease.

Bilirubin

Bilirubin is the water-insoluble product of heme metabolism that is taken up by hepatocytes and conjugated with glucuronic

[a] Portions previously published in Poterucha JJ. Fulminant hepatic failure. In: Johnson LR, editor. Encyclopedia of gastroenterology. Vol 2. Amsterdam: Elsevier Academic Press; c2004. p. 70-4; Poterucha JJ. Hepatitis. In: Bland KI, Sarr MG, Buchler MW, Csendes A, Garden OJ, Wong J, editors. General surgery: principles and international practice. 2nd edition. London (Eng): Springer; 2009. p. 921-32; and Poterucha JJ, Gunneson TJ. Liver biopsy and paracentesis. In: Talley NJ, Lindor KD, Vargas HE, editors. Practical gastroenterology and hepatology: liver and biliary disease. Oxford (UK): Wiley-Blackwell; c2010. p. 80-6. Used with permission.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; MELD, Model for End-stage Liver Disease; MRCP, magnetic resonance cholangiopancreatography

acid to form monoglucuronides and diglucuronides through the activity of the enzyme uridine diphosphate glucuronosyltransferase. Conjugation makes bilirubin water-soluble, allowing it to be excreted into the bile canaliculus. The serum concentration of bilirubin is measured in direct (conjugated) and indirect (unconjugated) fractions. Diseases characterized by overproduction of bilirubin, such as hemolysis or resorption of a hematoma, are characterized by hyperbilirubinemia that is 20% or less conjugated bilirubin. Hepatocyte dysfunction or impaired bile flow produces hyperbilirubinemia that is usually 20% to 80% conjugated bilirubin. Patients with an inherited disorder of bilirubin excretion into the canaliculus, such as Dubin-Johnson syndrome or Rotor syndrome, have hyperbilirubinemia that is more than 80% conjugated. Because conjugated bilirubin is water-soluble and may be excreted in urine, patients with conjugated hyperbilirubinemia may note dark urine. In these patients, the stools are lighter in color because of the absence of bilirubin pigments.

Prothrombin Time and Albumin

Prothrombin time and serum albumin are commonly used markers of liver synthetic function. Abnormalities of prothrombin time and albumin imply severe liver disease and should prompt immediate evaluation. Prothrombin time is a measure of the activity of coagulation factors II, V, VII, and X, all of which are synthesized in the liver. These factors are dependent also on vitamin K for synthesis. Vitamin K deficiency may be caused by antibiotics, prolonged fasting, small-bowel mucosal disorders such as celiac disease, or severe cholestasis with an inability to absorb fat-soluble vitamins. Hepatocellular dysfunction is characterized by an inability to synthesize clotting factors despite adequate stores of vitamin K. A simple way to differentiate vitamin K deficiency from hepatocellular dysfunction in a patient with a prolonged prothrombin time is to administer vitamin K. Administration of parenteral vitamin K improves prothrombin time within 24 hours in a vitamin K–deficient patient but has little effect if the prolonged prothrombin time is due to liver disease with poor hepatocellular function.

Because albumin has a half-life of 21 days, decreases due to liver dysfunction do not occur suddenly; however, the serum level of albumin can decrease relatively quickly in a patient who has an acute inflammatory illness such as bacteremia. This rapid decrease likely is caused by the release of cytokines, which accelerate the metabolism of albumin. Other causes of hypoalbuminemia include urinary or gastrointestinal tract losses, and these should be considered in a patient who has hypoalbuminemia but not overt liver disease.

Platelet Count and Other Tests

Although most patients with significant liver injury have abnormalities of liver enzymes, some patients with cirrhosis may have normal test results and preserved liver function. A decreased platelet count due to hypersplenism may be a clue to the presence of significant liver injury, and the presence of thrombocytopenia mandates exclusion of portal hypertension even when the results of other liver tests are normal. Most patients with thrombocytopenia due to portal hypertension have splenomegaly and, often, other features of portal hypertension such as esophageal varices. When performed in patients with thrombocytopenia with hypersplenism, bone marrow examination usually shows an increased number of megakaryocytes. Measurement of inflammatory markers such as γ-globulin and IgG levels can be helpful to assess for inflammatory states, especially autoimmune hepatitis.

Table 22.1. Child-Turcotte-Pugh Score

	Number of Points[a]		
Measure	*1*	*2*	*3*
Encephalopathy	None	Stage 1 or 2	Stage 3 or 4
Ascites	None	Mild or moderate	Severe
Bilirubin, mg/dL	<2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

Abbreviation: INR, international normalized ratio.
[a] Interpretation: class A, 5-6 points; class B, 7-9 points; class C, 10-15 points.

Scoring Systems to Assess Liver Disease Severity

The Child-Turcotte-Pugh score (Table 22.1) uses encephalopathy, ascites, bilirubin, albumin, and prothrombin time (or international normalized ratio). The measurement of ascites and encephalopathy is subjective, leading to significant interobserver variation.

The Model for End-stage Liver Disease (MELD) is based on objective measurements: Prothrombin time (or international normalized ratio) and bilirubin and creatinine levels are used to prioritize patients for deceased donor liver transplant. In addition, the MELD score is useful for assessing surgical risk for patients with cirrhosis and for providing prognostic information for patients with alcoholic hepatitis. Addition of the serum sodium level to the calculation enhances the prognostic accuracy of the MELD score. A MELD score calculator is available at the following website: http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-na-model.

Hepatocellular Disorders

Acute Hepatitis

Diseases that affect primarily hepatocytes are characterized predominantly by increased levels of aminotransferases. Some authors have suggested that reference values validated by laboratories are too high, but the proposed new cutoffs probably would identify patients with only minimal liver disease and have not yet been widely endorsed. Hepatitis is differentiated into acute (generally <3 months) or chronic. Acute hepatitis may be accompanied by malaise, anorexia, abdominal pain, and jaundice. Common causes of acute hepatitis are listed in Table 22.2.

The pattern of increase in aminotransferase levels may be helpful in making a diagnosis. Acute hepatitis caused by viruses or drugs usually produces a marked increase in aminotransferase levels (often >1,000 U/L). Aminotransferase levels of more than 5,000 U/L usually are due to acetaminophen hepatotoxicity, ischemic hepatitis (shock liver), or hepatitis caused by unusual viruses, such as herpesvirus. Ischemic hepatitis occurs after an episode of hypotension and is seen most often in patients with preexisting cardiac dysfunction. Aminotransferase levels increase quickly and improve within a few days. Another cause of a transient increase in aminotransferase levels is an acute increase in intrabiliary pressure that usually is due to a common bile duct stone. These increases can be as high as 1,000 U/L, but the levels decrease dramatically within 24 to 48 hours. In patients with pancreatitis, a transient increase in AST or ALT is suggestive of gallstone pancreatitis. Alcoholic hepatitis is characterized by more modest increases in aminotransferase levels, nearly always less than 400 U/L, with an AST:ALT ratio greater than 2:1. As long as muscle injury has been excluded, the higher the AST:ALT

Table 22.2. Common Causes of Acute Hepatitis

Disease	*Clinical Clue*	*Diagnostic Test*
Hepatitis A	Exposure history	IgM anti-HAV
Hepatitis B	Risk factors	HBsAg, IgM anti-HBc
Drug-induced	Compatible medication	Improvement after agent is withdrawn
Alcoholic hepatitis	History of alcohol excess, AST:ALT >2:1, AST <400 U/L	Liver biopsy, improvement with abstinence
Ischemic hepatitis	History of severe hypotension	Rapid improvement of aminotransferase levels

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen.

ratio, the more likely a patient is to have alcoholic liver disease. Patients with alcoholic hepatitis frequently have an increase in bilirubin level that is out of proportion to the increase in aminotransferase levels.

When common causes of acute hepatitis have been excluded, considerations should include cytomegalovirus or Epstein-Barr virus, hepatitis E, severe cardiovascular disease, seronegative autoimmune hepatitis, and unrecognized drug- or toxin-induced liver injury.

Chronic Hepatitis

Diseases that produce sustained (>3 months) increases in aminotransferase levels are included in the category of chronic hepatitis. The increase in aminotransferase levels is more modest (1.5-5 times the upper limit of the reference range) than that in acute hepatitis. Generally, ALT increases more than AST. As chronic liver diseases such as hepatitis C and nonalcoholic fatty liver disease become more advanced, the AST sometimes becomes more elevated than the ALT, although the AST:ALT ratio usually remains less than 2:1. The most important and common disorders that cause chronic hepatitis are listed in Table 22.3.

Risk factors for hepatitis C include a history of intravenous drug use or exposure to blood products. Most patients with hepatitis B are from an endemic area such as parts of Asia or Africa or have a history of illegal drug use or multiple sexual contacts. Patients with nonalcoholic fatty liver disease are usually obese and have diabetes mellitus or hyperlipidemia. A complete history is needed to help diagnose drug-induced or alcohol-induced liver disease. Autoimmune hepatitis may manifest as acute or chronic hepatitis. Patients usually have an ALT serum level of 200 to 800 U/L, higher than that in other disorders that cause chronic hepatitis. Autoantibodies, hypergammaglobulinemia, and other autoimmune disorders are helpful clues to the diagnosis of autoimmune hepatitis.

When the most common causes of liver disease have been excluded, other diseases that should be considered are chronic drug-induced liver injury, celiac disease, and nonalcoholic fatty liver disease that is not apparent on imaging. About 30% to 50% of patients with celiac disease have elevated aminotransferase levels, and these abnormalities often improve with a gluten-free diet. Celiac disease may also accompany immune-mediated liver diseases such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. Chronic liver disease due to drug-induced liver injury is rare. Thyroid disorders can elevate liver test results through an unknown mechanism.

Cholestatic Disorders

Diseases that affect predominantly the biliary system are termed *cholestatic diseases*. These can affect the microscopic ducts (eg, primary biliary cirrhosis), large bile ducts (eg, pancreatic cancer obstructing the common bile duct), or both (eg, primary sclerosing cholangitis). In these disorders, the predominant abnormality is the alkaline phosphatase level. Although diseases that produce increased bilirubin levels are often called "cholestatic," severe hepatocellular injury, as in acute hepatitis, also produces hyperbilirubinemia because of hepatocellular dysfunction. Causes of cholestasis are listed in Table 22.4.

Primary biliary cirrhosis usually occurs in women and can cause fatigue or pruritus. Of the patients with primary sclerosing cholangitis, 70% to 80% also have ulcerative colitis. Patients with primary biliary cirrhosis or primary sclerosing cholangitis often are asymptomatic but may have jaundice, fatigue, or pruritus. Large bile duct obstruction often is due to stones or to benign or malignant strictures. Acute bile duct obstruction from a stone is accompanied by abdominal pain and often fever and may produce marked increases in aminotransferase levels. Because alkaline phosphatase must be synthesized before excretion, acute biliary obstruction may not cause an elevated alkaline phosphatase level. Gradual biliary obstruction, such as that caused by a malignant stricture, is initially painless and not accompanied by fever. Infiltrative disorders such as amyloidosis, sarcoidosis, or lymphoma may produce a markedly increased alkaline phosphatase level with a normal bilirubin concentration. Any systemic inflammatory process such as infection or immune disorder may produce nonspecific liver test result abnormalities. The abnormalities usually show a mixed cholestatic (alkaline phosphatase) and hepatocellular (ALT or AST) pattern.

Jaundice

Jaundice is visibly evident hyperbilirubinemia and occurs when the bilirubin concentration is more than 2.5 mg/dL. A common

Table 22.3. Common Causes of Chronic Hepatitis

Disease	*Clinical Clue*	*Diagnostic Test*
Hepatitis C	Risk factors	Anti-HCV, HCV RNA
Hepatitis B	Risk factors	HBsAg
Nonalcoholic fatty liver disease	Obesity, diabetes mellitus, hyperlipidemia	Ultrasonography, liver biopsy
Alcoholic liver disease	History, AST:ALT>2:1	Liver biopsy, improvement with abstinence
Autoimmune hepatitis	ALT 200-1,500 U/L, usually female, other autoimmune disease	Antinuclear or anti–smooth muscle antibody, biopsy

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Table 22.4. Common Causes of Cholestasis

Disease	*Clinical Clue*	*Diagnostic Test*
Primary biliary cirrhosis	Middle-aged woman	Antimitochondrial antibody
Primary sclerosing cholangitis	Association with ulcerative colitis	ERCP, MRCP
Large bile duct obstruction	Jaundice and pain are common	Ultrasonography, ERCP, MRCP
Drug-induced	Compatible medication or timing	Improvement after agent is withdrawn
Infiltrative disorder	History of malignancy, amyloidosis, sarcoidosis	Ultrasonography, computed tomography
Inflammation-associated	Symptoms of underlying inflammatory disorder	Blood cultures, appropriate antibody tests

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

disorder that produces unconjugated hyperbilirubinemia (but not usually jaundice) is Gilbert syndrome due to an inherited deficiency of uridine diphosphate glucuronosyltransferase. Total bilirubin is generally less than 3.0 mg/dL, whereas direct bilirubin is 0.3 mg/dL or less. The bilirubin level usually is highest when a patient is ill or fasting. A presumptive diagnosis of Gilbert syndrome can be made in an otherwise well patient who has unconjugated hyperbilirubinemia, normal liver enzyme values, and a normal concentration of hemoglobin (to exclude hemolysis).

Direct hyperbilirubinemia can result from a nonobstructive condition or from an obstructive condition. Obstruction is suggested by abdominal pain, fever, or a palpable gallbladder (or a combination of these). Jaundice due to hepatocellular dysfunction is suggested by risk factors for viral hepatitis, recent ingestion of a potentially hepatotoxic drug, a bilirubin concentration of more than 15 mg/dL, and persistently high aminotransferase levels. In patients with resolving acute hepatitis, improvement in bilirubin concentration often lags behind the improvement in aminotransferase levels. In diseases resulting in large bile duct obstruction, extrahepatic and intrahepatic biliary dilatation can be identified on imaging studies, especially if the bilirubin concentration is more than 10 mg/dL and the patient has had jaundice for more than 2 weeks. Acute large bile duct obstruction, usually from a stone, may not cause dilatation of the bile ducts, and if the clinical suspicion is strong for bile duct obstruction even though ultrasonography or computed tomography shows normal-sized bile ducts, the biliary tree should be imaged with magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), or endoscopic ultrasonography.

General Approach to Abnormal Liver Test Results

An abnormal liver can usually be categorized into one of the clinical syndromes in Box 22.1, although overlap among these categories is considerable. The approach to patients with acute hepatitis, chronic hepatitis, cholestasis, and jaundice is outlined above. Patients with a "first-time," often incidental, increase in liver enzyme levels are usually asymptomatic. Observation is reasonable, with the test repeated in a few months, as long as 1) no risk factors for liver disease are identified, 2) liver enzyme levels are less than 3 times normal, 3) liver function is preserved, and 4) the patient feels well. About 30% of patients with incidental elevations of liver test results will have normal values on subsequent testing. If the subsequent test results are still abnormal, the patient's condition fits the category of chronic hepatitis or cholestasis and appropriate evaluation should be initiated. A similar approach can be taken with incidentally discovered abnormal results from patients who are taking medications that only rarely cause liver disease.

Box 22.1. Abnormal Liver Test Results: Clinical Syndromes

"First-time" increase in liver enzymes

Acute hepatitis

Chronic hepatitis

Cholestasis without hepatitis or jaundice

Jaundice

Cirrhosis or portal hypertension

Patients also may present with cirrhosis or portal hypertension. Most patients with portal hypertension have cirrhosis, although occasionally patients present with noncirrhotic portal hypertension that is idiopathic or due to portal vein thrombosis. The evaluation of a patient who has cirrhosis is similar to that of a patient who has chronic hepatitis and cholestasis (as discussed above). In patients with α_1-antitrypsin deficiency, genetic hemochromatosis, alcoholic liver disease, or nonalcoholic fatty liver disease, cirrhosis is frequently the first manifestation of liver disease. If clinical and imaging features strongly suggest cirrhosis, confirmatory liver biopsy is not necessary.

Liver Biopsy

Technique and Safety

Most liver biopsies are performed percutaneously and guided by imaging such as ultrasonography. In patients with ascites or coagulopathy, excellent specimens may also be obtained with transvenous access from the jugular vein. If open or laparoscopic abdominal surgery is necessary for another indication, biopsy specimens may also be obtained under direct visualization. The most common complication of liver biopsy is pain, which can usually be controlled with simple analgesics. The most serious risk is bleeding, which occurs in 0.1% to 0.3% of all liver biopsies. Bleeding usually subsides without the need for transfusion or other intervention. Persistent bleeding may rarely require transarterial embolization. Other complications of liver biopsy are bile leaks, perforation of an abdominal organ, and pneumothorax. Severe pain following liver biopsy is suggestive of a bile leak.

General Utility

In patients with acute liver disease, a diagnosis is usually forthcoming with the help of the clinical history and blood tests for infections and inherited and metabolic disorders; therefore, biopsy is generally not performed. Occasionally, liver biopsy is needed to help in the diagnosis of a sudden onset of autoimmune hepatitis, drug-induced liver injury, diffuse intrahepatic malignancy not identified on imaging, Wilson disease, alcoholic liver

disease when clinical history is uncertain, and unusual infections such as herpes or histoplasmosis. Occasionally, liver biopsy may detect clinically unsuspected chronic liver disease in a patient presenting with acute hepatitis.

Liver biopsies are frequently used when patients have chronic liver disease; however, histopathologic findings are often nonspecific. A common report might include a lymphoplasmacytic portal infiltrate consistent with viral, drug, or autoimmune hepatitis. Clinical information is then required to help differentiate a cause. When the liver biopsy is done for diagnostic reasons, the pathologist and clinician should communicate, when possible, to allow an exchange of relevant information. This kind of dialogue is much more effective than if the clinician merely relies on the biopsy report or the pathologist relies on printed clinical information, much of which may be incomplete. Liver biopsy allows assessment of fibrosis, which can help with prognostication and treatment decisions.

Patients with long-term liver enzyme elevations and negative or normal results on blood tests are frequently referred to hepatology clinics for evaluation for causes of chronic liver disease. Studies incorporating liver biopsy show that most of these patients have nonalcoholic fatty liver disease with mild histologic changes. About 19% of patients have normal liver histology or minimal abnormalities. Predictors of minimal changes are female sex and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) less than 25. Predictors of significant fibrosis are tobacco use, BMI greater than 25, and presence of diabetes mellitus.

Alternatives to Liver Biopsy

The problems with liver biopsy are expense, risk, and sampling variability. Variations of 1 or 2 stages of fibrosis can be seen in up to 20% to 30% of patients undergoing liver biopsy from 2 different sites. Therefore, alternatives to liver biopsy are being studied and include various combinations of biochemical blood tests and percutaneous ultrasonographically guided or magnetic resonance imaging–guided measurements of liver "stiffness" with elastography. These techniques have not replaced histopathologic assessment, but they are being actively pursued and may become more accepted in the future. Serum fibrosis markers are generated from a panel of blood tests and are used in some centers.

Acute Liver Failure

Definition and Etiology

Acute liver failure is the development of liver failure, including coagulopathy and encephalopathy, within 28 weeks after the onset of symptoms in a patient without a previous history of chronic liver disease. Patients with an acute presentation of Wilson disease or a flare of hepatitis B may be still characterized as having acute liver failure even if they have histologic features of chronic liver injury. About 2,000 cases of acute liver failure occur annually in the United States. Because many of the patients are young and previously healthy, a poor outcome of this relatively unusual condition is particularly tragic.

Determining the cause of acute liver failure is important for 2 reasons: 1) specific therapy may be available, as for acetaminophen hepatotoxicity or herpes hepatitis, and 2) the prognosis differs depending on the cause. For instance, the spontaneous recovery rate for patients with acute liver failure due to acetaminophen or hepatitis A is more than 50%; consequently, a more cautious approach would be advised before proceeding with liver transplant. In comparison, spontaneous recovery from acute liver failure due to Wilson disease is unusual and early liver transplant would be recommended. In the United States, the most common identifiable causes are acetaminophen hepatotoxicity, idiosyncratic drug reactions, Wilson disease, hepatitis B, and ischemia (Table 22.5). Acetaminophen adducts have also been identified in about 20% of patients with idiopathic acute liver failure, suggesting that acetaminophen hepatotoxicity may have a role in this patient subset. Liver biopsy is not generally necessary for patients with acute liver failure. If the cause of acute liver failure cannot be determined from the history and blood tests, biopsy can be considered to exclude malignancy and autoimmune hepatitis.

Table 22.5. Causes of Acute Liver Failure in the United States, 1998-2007

Cause	*Frequency, %*
Acetaminophen	46
Idiopathic	14
Other drugs	11
Hepatitis B	7
Wilson disease	7
Autoimmune	5
Ischemia	4
Hepatitis A	3
Other identified cause	2

Presentation

The presenting symptoms of patients with acute liver failure are usually those of acute hepatitis, including malaise, nausea, and jaundice. Hepatic encephalopathy is a required feature of the syndrome, and manifestations may range from subtle mental status changes, such as difficulty with concentration, to coma (Table 22.6). Because encephalopathy in a patient with acute liver disease is an ominous sign, the mental status of patients with acute hepatitis should be assessed frequently. Laboratory features are consistent with severe liver dysfunction. Aminotransferase levels are variably increased, although they usually are more than 1,000 U/L. Acetaminophen hepatotoxicity usually causes ALT to be more than 3,500 U/L. Fulminant Wilson disease is characterized by only modest increases in aminotransferase levels and a normal or only minimally increased alkaline phosphatase level despite clinical evidence of liver failure, such as a prolonged prothrombin time and high bilirubin concentration.

The encephalopathy associated with acute liver failure, unlike that of chronic liver disease, has a propensity to progress to cerebral edema. The mechanisms for the development of cerebral edema have not been clarified but may involve disruption of the blood-brain barrier and interference with mechanisms of cellular osmolarity. Clinically, the encephalopathy often is associated with a marked

Table 22.6. Stages of Hepatic Encephalopathy

Stage	*Features*
I	Changes in behavior, with minimal change in level of consciousness
II	Gross disorientation, gross slowness of mentation, drowsiness, asterixis, inappropriate behavior, maintenance of sphincter tone
III	Sleeping most of the time, arousable to vocal stimuli, marked confusion, incoherent speech
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

increase in the serum level of ammonia, although alterations in unidentified neurotransmitters likely are involved in causing mental status changes. Ammonia levels of more than 200 µmol/L have been associated with intracranial hypertension and a poor outcome.

Cerebral edema is estimated to cause about 20% of the deaths of patients with acute liver failure. Cerebral edema leads to death by causing brain ischemia and cerebral herniation. Patients with acute liver failure are predisposed to infections likely due to severe illness and the need for numerous interventions and monitoring. The clinical features typical of infection, such as fever and leukocytosis, may not occur in patients with acute liver failure, so a high level of awareness for infection needs to be maintained. Any clinical deterioration should mandate a search for infection, and the threshold for antimicrobial therapy should be low.

Hypoglycemia occurs frequently and is a poor prognostic sign. It is likely due to both inadequate degradation of insulin and diminished production of glucose by the diseased liver.

A hyperdynamic circulation and a decrease in systemic vascular resistance are seen in patients with acute liver failure. These features may be well tolerated by patients, but occasionally hemodynamic compromise can develop. Monitored parameters may mimic sepsis. Fluid resuscitation usually is necessary, although caution is advised because the administration of excessive fluid may worsen intracranial pressure.

Renal and electrolyte abnormalities occur because of underlying disease such as Wilson disease, functional renal failure due to sepsis or hepatorenal syndrome, or acute tubular necrosis. Renal dysfunction is particularly common in acetaminophen-induced acute liver failure. Monitoring of electrolytes, including sodium, potassium, bicarbonate, magnesium, and phosphorus, is important, and the presence of acidosis is a risk factor for poor outcome in acute liver failure and has been incorporated into prognostic models.

Management

The appearance of encephalopathy precedes cerebral edema; therefore, patients with acute hepatitis and evidence of liver failure need to be monitored carefully for mental status changes. Patients with encephalopathy should receive lactulose, although this agent is not as effective in acute liver failure as in chronic liver disease and may not prevent cerebral edema from developing later. Patients with stage II encephalopathy usually are admitted to an intensive care unit for close monitoring of mental status and vital signs. Sedatives should be avoided initially to allow close monitoring of mental status. Computed tomography of the head is performed to exclude an alternative cause of mental status changes.

Patients who reach stage III encephalopathy are at considerable risk for progression to cerebral edema. Because clinical signs and computed tomography are insensitive for detecting increased intracranial pressure, many centers institute intracranial pressure monitoring when patients reach stage III encephalopathy. Endotracheal intubation and mechanical ventilation usually precede placement of the intracranial pressure monitor. Various monitors are used, but infection and bleeding can complicate any monitoring. The goal of intracranial pressure monitoring is to allow treatment of high pressure and to identify which patients are too ill for liver transplant because of a prolonged period of excessively high intracranial pressure. Generally, the goal is to maintain intracranial pressure less than 40 mm Hg and cerebral perfusion pressure (the difference between mean arterial pressure and intracranial pressure) between 60 and 100 mm Hg. Excessively high cerebral perfusion pressures (>120 mm Hg) can increase cerebral edema.

Maneuvers that cause straining, including endotracheal suctioning, should be avoided or limited. Paralyzing agents and sedatives may be necessary, although they may limit further assessment of neurologic status. If intracranial pressure is more than 20 mm Hg or cerebral perfusion pressure less than 60 mm Hg, the following steps are advised: elevation of the head to 20°, hyperventilation to a $PaCO_2$ of 25 mm Hg, and administration of mannitol (if renal function is intact). Barbiturate-induced coma can be used for refractory cases. A prolonged increase in intracranial pressure above mean arterial pressure may signify brain death and generally is a contraindication to liver transplant. A sudden decrease in intracranial pressure may indicate brain herniation.

In patients with acute liver failure, the prolonged prothrombin time is a simple noninvasive measure to follow, and coagulopathy is not corrected unless there is bleeding or an intervention is planned (eg, placement of a monitoring device). If bleeding occurs or an invasive procedure is necessary, fresh frozen plasma usually is administered first, although platelets, fibrinogen, and even recombinant activated factor VII may be necessary. Continuous infusion of 5% or 10% dextrose is used to keep the plasma glucose level between 100 and 200 mg/dL. The plasma glucose level should be monitored at least twice daily. Both bacteremia and fungemia are sufficiently frequent that periodic blood cultures are advised and prophylaxis with antimicrobials may be initiated, although this practice has not been shown to affect survival.

One recent randomized trial suggested that administration of *N*-acetylcysteine may be beneficial in some patients who have acute liver failure even when acetaminophen hepatotoxicity has been excluded. Patients with early-stage encephalopathy treated with *N*-acetylcysteine had better transplant-free survival than untreated patients.

Models to predict the outcome of acute liver failure have been developed to facilitate the optimal timing of liver transplant before the patient becomes so ill that transplant is contraindicated yet still allow time for spontaneous recovery. The most well-known and widely used model is the King's College criteria (Box 22.2). Acute liver failure is the indication for 6% of liver transplants in the United States. Even though 1-year survival with

Box 22.2. King's College Criteria for Liver Transplant in Fulminant Liver Failure[a]

1. **Fulminant liver failure due to Wilson disease or Budd-Chari syndrome**
2. **Acetaminophen-induced if either of the following are met:**
   a. pH <7.3 at 24 h after overdose
   b. Creatinine >3.4 mg/dL, prothrombin time >100 s, and stage III or IV encephalopathy
3. **Non–acetaminophen-induced if either of the following are met:**
   a. INR >6.5 *or*
   b. Any 3 of the following: INR >3.5, >7 d from jaundice to encephalopathy, indeterminate or drug-induced cause, age <10 y, age >40 y, bilirubin >17.5 mg/dL

Abbreviation: INR, international normalized ratio.

[a] Any 1 of the 3 criteria.

transplant for acute liver failure is lower than that for transplant for other indications, outcomes are an improvement over the dismal survival rates for patients with acute liver failure who meet poor prognostic markers such as the King's College criteria, and long-term survival after transplant is excellent.

Suggested Reading

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23

Viral Hepatitis[a]

JOHN J. POTERUCHA, MD

Viral infections are important causes of liver disease worldwide. The 5 primary hepatitis viruses that have been identified are A, B, C, D (or delta), and E. Other viruses, such as cytomegalovirus and Epstein-Barr virus, also can result in hepatitis as part of a systemic infection. In addition, medications, toxins, autoimmune hepatitis, or Wilson disease may cause acute or chronic hepatitis.

It is useful to divide hepatitis syndromes into acute and chronic forms. Acute hepatitis can last from a few weeks to 6 months and is often accompanied by jaundice. Symptoms of acute hepatitis tend to be similar regardless of cause and include anorexia, malaise, dark urine, fever, and mild abdominal pain. In chronic hepatitis, patients are often asymptomatic but may complain of fatigue. Occasionally, they have manifestations of advanced liver disease (ascites, variceal bleeding, or encephalopathy) at the initial presentation with chronic hepatitis. Each hepatitis virus causes acute hepatitis, but only hepatitis B, C, and D viruses can cause chronic hepatitis.

The purpose of this chapter is to review the primary hepatitis viruses. More comprehensive discussions of acute hepatitis are found in other chapters. The 4 common hepatitis viruses are compared in Table 23.1, and the disease burden of the 3 most important viruses in the United States is summarized in Table 23.2.

[a] Portions previously published in Poterucha JJ. Hepatitis. In: Bland KI, Sarr MG, Buchler MW, Csendes A, Garden OJ, Wong J, editors. General surgery: principles and international practice. 2nd Ed. London (England): Springer-Verlag; c2009. p. 921-32. Used with permission.

Abbreviations: ALT, alanine aminotransferase; anti-HAV, antibody to hepatitis A virus; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; SVR, sustained virologic response

Hepatitis A

Epidemiology

The incidence of acute hepatitis A virus (HAV) infection is decreasing in the United States. Common routes of transmission of HAV are ingestion of contaminated food or water and contact with an infected person. Groups at particularly high risk include people living in or traveling to underdeveloped countries, children in day care centers, men who have sex with men, and perhaps persons who ingest raw shellfish. The incubation period for HAV is 2 to 6 weeks.

Clinical Presentation and Natural History

The most important determinant of the severity of acute hepatitis A is the age at which infection occurs. Persons infected when younger than 6 years have nonspecific symptoms that rarely include jaundice. Adolescents or adults who acquire HAV infection usually have jaundice. Hepatitis A is almost always a self-limited infection. There may be a prolonged cholestatic phase characterized by persistence of jaundice for up to 6 months. Rarely, acute hepatitis A manifests as acute liver failure that may require liver transplant. HAV does not cause chronic infection and should not be in the differential diagnosis of chronic hepatitis.

Diagnostic Tests

The diagnosis of acute hepatitis A is established by the presence of IgM antibody to hepatitis A virus (anti-HAV), which appears at the onset of the acute phase of the illness and becomes

Table 23.1. Comparison of the 4 Primary Hepatitis Viruses

Feature	*HAV*	*HBV*	*HDV*	*HCV*
Incubation, d	15-50	30-160	Unknown	14-160
Jaundice	Common	30% of patients	Common	Uncommon
Course	Acute	Acute or chronic	Acute or chronic	Acute or chronic
Transmission	Fecal-oral	Parenteral	Parenteral	Parenteral
Test for diagnosis	IgM anti-HAV	HBsAg	Anti-HDV	HCV RNA

Abbreviations: anti-HAV, antibody to hepatitis A virus; anti-HDV, antibody to hepatitis D virus; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus.

Table 23.2. Clinical Effects of Hepatitis Viruses in the United States[a]

Feature	*HAV*	*HBV*	*HCV*
Acute hepatitis, No. of clinical cases annually	11,000	12,000	2,900
Fulminant hepatitis, No. of deaths annually	50	100	Rare
Chronic hepatitis, No. of clinical cases annually	0	800,000-1.4 million	2.7-3.9 million
Chronic liver disease, No. of deaths annually	0	3,000	12,000

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a] Data from the Centers for Disease Control and Prevention (2008 data).

undetectable in 3 to 6 months. The IgG anti-HAV also becomes positive during the acute phase, but it persists for decades and is a marker of immunity from further infection. A patient with IgG anti-HAV, but not IgM anti-HAV, has had an infection in the remote past or has been vaccinated.

Treatment

The treatment of acute hepatitis A is supportive. For those exposed to an infected person or contaminated food, postexposure prophylaxis with hepatitis A vaccine or immune serum globulin (or both) is advised, depending on the patient's age and overall health status.

Prevention

Immunization with hepatitis A vaccine is recommended for all children at 12 months of age. Hepatitis A vaccine should be offered also to travelers to areas with an intermediate or high prevalence of hepatitis A, to men who have sex with men, to intravenous drug users, to recipients of clotting factor concentrates, and to patients with chronic liver disease.

Hepatitis B

Epidemiology

Hepatitis B virus (HBV) is a DNA virus that causes about 30% of the cases of acute viral hepatitis and 15% of the cases of chronic viral hepatitis in the United States. Most chronically infected persons in the United States are immigrants from Asia and Africa, where infection is acquired at birth or in early childhood. Major risk factors for adult disease acquisition in the United States are sexual contact with an infected person and intravenous drug use.

Clinical Presentation and Natural History

The incubation period after HBV infection ranges from 60 to 150 days. About 30% of adolescents or adults with acute hepatitis B are icteric. Complete recovery with subsequent lifelong immunity occurs in 95% of infected adults. *Chronic infection*, defined as persistence of hepatitis B surface antigen (HBsAg) for more than 6 months, develops in about 5% of infected adults. Immunosuppressed persons with acute HBV infection are more likely to become chronically infected, presumably because of an insufficient immune response against the virus.

Patients with chronic hepatitis B infection present in 1 of 4 phases (Figure 23.1). An *immune tolerant phase* is recognized in many Asian patients who are infected perinatally. This phase, usually encountered in patients younger than 35 years, is characterized by the presence of hepatitis B e antigen (HBeAg) and very high HBV DNA levels yet normal levels of alanine aminotransferase (ALT). Generally, liver biopsy specimens from these patients show minimal changes except for ground-glass hepatocytes. The immune tolerant phase evolves under immune pressure into the *HBeAg-positive chronic hepatitis B phase*, characterized by increased ALT levels, persistence of HBeAg, and more than 10^4 IU/mL of HBV DNA. Active inflammation and often fibrosis, seen in liver biopsy specimens, lead to progressive liver injury. At a rate of about 10% per year, patients mount enough of an immune response to achieve a decrease in ALT levels, clearance of HBeAg and development of antibody to HBeAg (seroconversion), and a decrease in HBV DNA to less than 10^4 IU/mL. The resulting *inactive carrier phase* usually is not accompanied by progressive liver damage. In cross-sectional studies, about 60% of patients with chronic hepatitis B are in the inactive carrier phase. Many patients remain in this phase for many years and have a better prognosis than those with active liver inflammation and HBV DNA levels of more than 10^4 IU/mL.

About one-third of inactive carriers have a reactivation of active hepatitis characterized by abnormal ALT levels and HBV DNA levels of more than 10^4 IU/mL. This may be associated with a reversion to the HBeAg-positive state, but more commonly it is due to a precore or core promoter variant. This *HBeAg-negative chronic hepatitis B phase* is associated with progression of liver damage. Patients with HBeAg-negative chronic hepatitis B are more likely to have a fluctuating course than patients with HBeAg-positive chronic hepatitis B. Also, the patients generally are older and have more advanced fibrosis because HBeAg-negative chronic hepatitis B tends to occur later in the course of infection.

Patients with chronic hepatitis B may experience spontaneous flares of disease characterized by markedly abnormal ALT

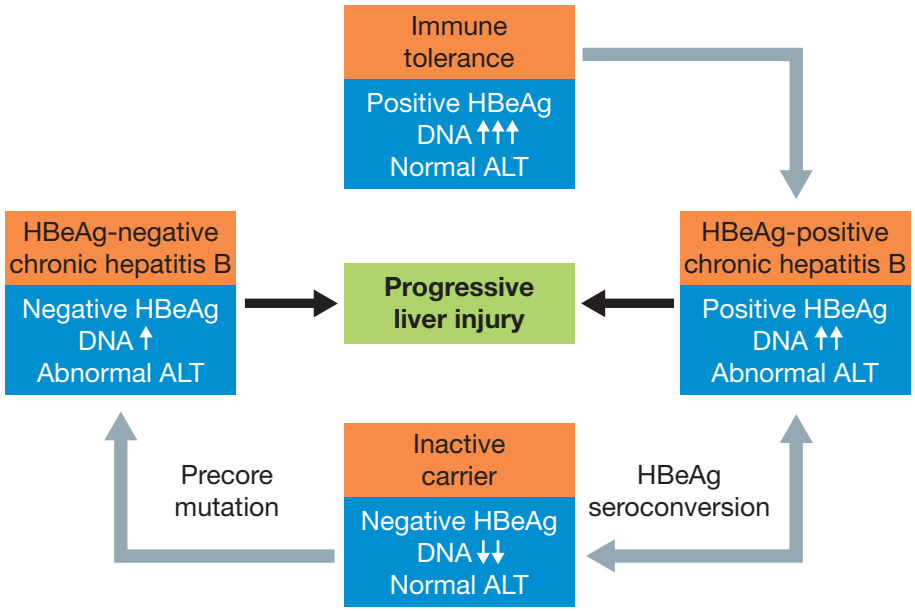

Figure 23.1. Phases of Chronic Hepatitis B Virus Infection. Black arrows, histopathologic changes; gray arrows, changes in serologic markers between phases. White arrows, increase or decrease of DNA level (↑, low increase; ↑↑, moderate increase; ↓↓, moderate decrease; ↑↑↑, high increase). ALT indicates alanine aminotransferase; HBeAg, hepatitis B e antigen. (Adapted from Pungpapong S, Kim WR, Poterucha JJ. Natural history of hepatitis B virus infection: an update for clinicians. Mayo Clin Proc. 2007 Aug;82[8]:967-75. Used with permission of Mayo Foundation for Medical Education and Research.)

levels, deterioration in liver function, and often seroconversion of HBeAg. The differential diagnosis for acute hepatitis in patients with chronic hepatitis B is listed in Table 23.3. Because disease activity changes in patients with chronic hepatitis B, even after years in the inactive carrier state, periodic monitoring with liver tests and hepatitis B markers is necessary. HBsAg clears spontaneously in about 1% of chronically infected patients annually.

In about 15% to 40% of patients with chronic HBV infection, serious sequelae develop—either decompensated liver disease or hepatocellular carcinoma. Factors associated with the development of cirrhosis are older age; coinfection with hepatitis C virus (HCV), human immunodeficiency virus (HIV), or hepatitis D virus (HDV); hepatitis B genotype C; longer duration of infection; high HBV DNA levels; and alcohol abuse. Many of these factors, including HBV DNA level, are associated also with an increased risk of hepatocellular carcinoma.

Patients with chronic hepatitis B and cirrhosis are at high risk for the development of hepatocellular carcinoma, and surveillance every 6 to 12 months is advised. Surveillance also is advised for patients without cirrhosis who meet 1 of the following criteria: family history of hepatocellular carcinoma, Asian man older than 40 years, Asian woman older than 50 years, black African older than 20 years, and persistent increase in ALT level together with an HBV DNA value of more than 10^4 IU/mL. The method of surveillance varies among centers, but many use ultrasonography at 6-month intervals with or without monitoring serum alpha fetoprotein levels.

Eight hepatitis B genotypes, labeled A through H, have been identified, and the genotype for a patient is determined largely by the country in which infection is acquired. All genotypes have been identified in the United States. In Asian patients, genotype B has a better prognosis than genotype C, including a higher rate of clearance of HBeAg, a slower rate of progression to cirrhosis, and a lower likelihood of the development of hepatocellular cancer.

Diagnostic Tests

A brief guide to serologic markers for hepatitis B is provided in Table 23.4. The interpretation of serologic patterns is shown in Table 23.5. Rarely, a patient with acute hepatitis B (usually with a severe presentation such as acute liver failure) lacks HBsAg and has only IgM antibody to hepatitis B core antigen (anti-HBc) as the marker for recent infection. Patients with an acute flare of chronic hepatitis B may redevelop IgM anti-HBc. Most patients with HBsAg have detectable serum levels of HBV DNA. HBV

Table 23.3. Causes of Acute Hepatitis in Patients With Chronic Hepatitis B

Cause	*Clinical Clues*
Spontaneous "reactivation" of hepatitis B	Seroconversion of HBeAg, reappearance of IgM anti-HBc
Flare due to immunosuppression	Chemotherapy, antirejection therapy, corticosteroids, anti–tumor necrosis factor agents
Induced by antiviral therapy	Interferon (common), oral agents (rare)
Superimposed infection with other viruses, especially hepatitis D virus	Exposure to hepatitis D virus (usually due to illicit drug use), hepatitis A virus, or hepatitis C virus
Other causes of acute hepatitis	History of alcohol excess, medications, illegal drugs

Abbreviations: anti-HBc, antibody to hepatitis B core antigen; HBeAg, hepatitis B e antigen.

Table 23.4. Hepatitis B Serologic Markers

Test	*Significance*
Hepatitis B surface antigen (HBsAg)	Current infection
Antibody to hepatitis B surface antigen (anti-HBs)	Immunity (immunization or resolved infection)
IgM antibody to hepatitis B core antigen (IgM anti-HBc)	Recent infection or "reactivation" of chronic infection
IgG antibody to hepatitis B core antigen (IgG anti-HBc)	Remote infection
Hepatitis B e antigen (HBeAg) or hepatitis B virus DNA >10^4 IU/mL (or both)	Active viral replication (high infectivity)

Table 23.5. Interpretation of Hepatitis B Serologic Patterns

HBsAg	*Anti-HBs*	*IgM anti-HBc*	*IgG anti-HBc*	*HBeAg*	*Anti-HBe*	*HBV DNA, IU/mL*	*Interpretation*
+	−	+	−	+	−	+	Acute infection or, less commonly, acute flare of chronic hepatitis B
−	+	−	+	−	±	−	Previous infection with immunity
−	+	−	+	−	−	−	Vaccination with immunity
+	−	−	+	−	+	<10^4	Hepatitis B inactive carrier state
+	−	−	+	+	−	>10^4	Chronic hepatitis B
+	−	−	+	−	+	>10^4	HBeAg-negative chronic hepatitis B (often "precore" or "core promoter" variants)

Abbreviations: anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

DNA levels greater than 10^4 IU/mL are associated with an increased risk of cirrhosis and hepatocellular carcinoma.

Occasionally, patients have IgG anti-HBc as the only positive hepatitis B serologic marker. A common explanation for a population without risk factors for disease acquisition is a false-positive test (the test is often repeatedly positive). Another explanation is a previous, resolved HBV infection in which the level of antibody to hepatitis B surface antigen (anti-HBs) has decreased below the limit of detection. This can be supported by demonstrating an anamnestic type of response to hepatitis B vaccine. Rarely, patients with hepatitis B may have HBsAg levels that are below the level of detection, so that IgG anti-HBc is the only marker of infection. Although the significance of this low-level infection is unclear, these patients can be identified by the presence of HBV DNA in serum or liver.

The accuracy of serologic and nucleic acid tests obviates the need for liver biopsy in the diagnosis of hepatitis B; however, liver biopsy is useful for grading inflammatory activity and determining the stage of fibrosis. Histologic features of hepatitis B are inflammation that is usually around the portal tract, variable fibrosis that initially is also portocentric, and the presence of ground-glass hepatocytes. *Ground-glass hepatocytes* are hepatocytes with cytoplasm that has a hazy, eosinophilic appearance. With immunostaining, these cells are positive for HBsAg (Figure 23.2). Even though liver biopsy is the gold standard for diagnosing cirrhosis, it generally is not necessary for patients who have other features of cirrhosis, such as portal hypertension.

Treatment

Generally, hepatitis B is treated if the patient is at risk for disease progression. This includes patients in the HBeAg-positive or HBeAg-negative chronic hepatitis B phases. Patients with compensated cirrhosis should be treated if the HBV DNA level is more than 2,000 IU/mL, and patients with decompensated cirrhosis should be treated if there is any detectable HBV level. Acute liver failure due to acute hepatitis B should be treated with one of the oral agents, although benefit is uncertain.

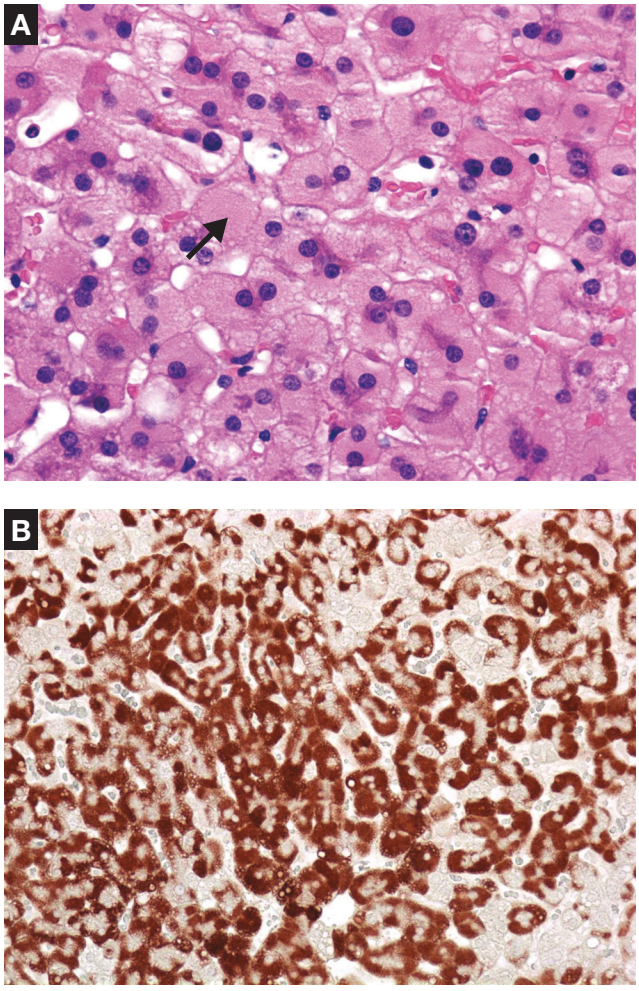

Figure 23.2. Liver Biopsy Specimen From Patient With Hepatitis B. A, Ground-glass hepatocyte (arrow). (Hematoxylin-eosin.) B, Immunostain for hepatitis B surface antigen showing positive staining of hepatocyte cytoplasm.

Patients with hepatitis B generally do not require liver biopsy before a decision about the need for treatment. Liver biopsy is helpful for patients who otherwise do not meet clear criteria for treatment. Liver biopsy also can be used to diagnose advanced fibrosis, which could mandate a change in management, such as evaluation for esophageal varices or surveillance for hepatocellular carcinoma.

Hepatitis B can be treated with peginterferon or one of the oral agents (lamivudine, adefovir, entecavir, telbivudine, or tenofovir). Peginterferon has replaced standard interferon because of its once-weekly dosing and perhaps better efficacy, and 1 year of treatment is advised. Seroconversion may occur months or even years after completion of treatment. Predictors of a greater likelihood of response to peginterferon include higher ALT level, lower HBV DNA level, shorter duration of disease, genotype A or B, and female sex. Patients treated with peginterferon may experience a flare of hepatitis (likely due to immune system activation) about 4 to 8 weeks after beginning treatment. Treatment should be continued despite this flare unless there is clinical or biochemical evidence of decompensation. Patients with Child-Turcotte-Pugh class B or C cirrhosis should not be treated with interferons because of the risk of precipitating decompensation with this flare. Adverse effects of peginterferon are common and are considered below (Hepatitis C section).

The oral agents are prescribed more frequently than peginterferon for chronic hepatitis B. They are compared in Table 23.6. These oral agents are well tolerated, and they are useful particularly in patients with decompensated cirrhosis, because these drugs may improve liver function. The flare of hepatitis that may occur during interferon therapy is unusual with the oral agents. Because of their high barrier to resistance, tenofovir and entecavir are the agents most commonly prescribed for hepatitis B. About 15% to 20% of HBeAg-positive patients treated with oral agents have seroconversion and are positive for antibody to HBeAg after 1 to 2 years of therapy; treatment should be continued for at least 6 months after seroconversion. Patients without seroconversion of HBeAg need to continue treatment indefinitely. Seroconversion of HBsAg with the oral agents is unusual; therefore, most patients with HBeAg-negative chronic hepatitis will require prolonged or even indefinite therapy.

The choice of therapeutic agent for hepatitis B depends on several factors. Peginterferon is reasonable for patients without cirrhosis who have an ALT level greater than 200 U/L and who are able to tolerate the numerous adverse effects of the drug. Peginterferon is most effective against hepatitis B genotypes A and B; thus, genotyping is advised for patients for whom peginterferon therapy is being considered. Entecavir or tenofovir is preferred for patients who have cirrhosis. Oral agents are preferred also for patients who are immunosuppressed, for example, after organ transplant or infection with HIV.

Patients who are HBsAg positive and need chemotherapy or immunosuppression are at risk for disease flare, and treatment with one of the oral agents is advised during therapy and for at least 6 months after therapy has been completed. Patients with isolated anti-HBc positivity are also at risk, although the risk is significantly smaller than for those who are HBsAg positive. Some groups suggest that patients with isolated anti-HBc positivity who are treated with rituximab or hematologic stem cell transplant are at high enough risk for disease activation to warrant prophylactic HBV treatment. For others with isolated anti-HBc positivity, monitoring of ALT and HBV DNA levels during immunosuppression therapy is advised, and treatment with oral agents should be given if HBV DNA becomes detectable.

For patients with end-stage liver disease or hepatocellular carcinoma due to hepatitis B, liver transplant results in excellent outcomes. Patients with hepatitis B who have HBeAg or high HBV DNA levels (or both) before liver transplant are at particularly high risk for recurrence after transplant. For these patients, oral agents are recommended before transplant, and a combination of hepatitis B immunoglobulin and an oral agent after transplant. Even among patients without detectable HBV DNA, recurrence rates are sufficiently high that most transplant groups still give one of the oral agents for both preoperative therapy and postoperative therapy.

Prevention

Hepatitis B immunoglobulin should be given to nonimmune household and sexual contacts of patients who have acute hepatitis B. All infants should receive hepatitis B vaccine. Neonates often acquire hepatitis B perinatally if the mother is infected; therefore, HBsAg testing should be performed on all pregnant women. Infants born to HBsAg-positive women should receive both hepatitis B immunoglobulin and hepatitis B vaccine. In addition, oral agents can be administered during the third trimester to pregnant women who have HBV DNA levels higher than 10^7 to 10^8 IU/mL. Tenofovir is a category B drug for pregnant women and is a safe choice for treatment during pregnancy.

Hepatitis D

HDV (or the delta agent) requires the presence of HBsAg to replicate. HDV infection can occur simultaneously with HBV (coinfection) or as a superinfection in persons with established hepatitis B. Hepatitis D is diagnosed with antibodies to HDV and should be suspected if a patient has acute hepatitis B or an acute exacerbation of chronic hepatitis B. In the United States, intravenous drug users are the group of HBV patients at highest risk for acquiring HDV. Although HDV does not commonly require

Table 23.6. Oral Agents for Treatment of Hepatitis B

Feature	*Lamivudine*	*Adefovir*	*Entecavir*	*Telbivudine*	*Tenofovir*
Monthly charge, $[a]	150	1,086	970	890	860
HBeAg seroconversion, % of patients	20	12	21	22	20
Loss of HBV DNA, % of patients	40	21	67	60	90
Resistance, % of patients	20 at 1 y 70 at 5 y	0 at 1 y 29 at 5 y	Naive: <1 at 2 y Lamivudine resistance: 7 at 1 y	4 at 1 y 21 at 2 y	None
Durability of response, % of responding patients	50-80	90	69	80	Unknown

Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.
[a] Data from http://cashcard.lc.healthtrans.com (2012).

treatment, peginterferon can be used with sustained virologic clearance in about 30% of treated patients.

Hepatitis C

Epidemiology

HCV is the cause of the most common chronic bloodborne infection in the United States, where an estimated 3 to 4 million persons are infected. Although the number of new cases of HCV infection is decreasing, the number of HCV-related deaths has continued to increase because of the propensity of the virus to cause chronic infection. HCV is a factor in 40% of all cases of chronic liver disease and is the leading indication for liver transplant.

Clinical Presentation and Natural History

The incubation period of HCV ranges from 2 to 23 weeks (mean, 7.5 weeks). Patients infected with HCV rarely present clinically with acute hepatitis, although retrospective studies have suggested that 10% to 20% of patients have an icteric illness with acute infection. Of those who acquire hepatitis C, chronic infection develops in 60% to 85% (Figure 23.3). Once chronic infection has been established, subsequent spontaneous loss of the virus is rare. Consequently, most patients with hepatitis C present with chronic hepatitis, with a mild to moderate increase in ALT levels. For patients with abnormal ALT levels, the degree of increase does not correlate with the histologic severity of disease.

Up to 30% of patients chronically infected with HCV have a persistently normal level of ALT. As a group, these patients generally have less aggressive histologic features and a lower risk of disease progression than patients with hepatitis C and abnormal ALT levels, but it is recommended that patients with normal ALT levels and patients with abnormal ALT levels be managed similarly and undergo biopsy when necessary to help make management decisions.

Nearly all mortality and most morbidity associated with hepatitis C are due to cirrhosis. In about 20% to 30% of patients with chronic hepatitis C, cirrhosis develops over a 20-year period (Figure 23.3). Factors that lead to a higher risk of advanced fibrosis are duration of infection, alcohol intake of more than 50 g daily, steatosis, coinfection with HIV or HBV, and male sex. Patients with cirrhosis due to HCV generally have had the disease longer than 20 years.

An important predictive factor for the development of cirrhosis is the severity of the histologic features of the liver at presentation. Liver biopsy specimens need to be interpreted with knowledge of the duration of infection (if known). Patients who have only mild portal hepatitis without fibrosis, despite many years of infection, have a significantly lower risk of progression to cirrhosis than those who have more advanced disease with a similar duration of infection. Histologic markers of more advanced disease include moderate degrees of inflammation and necrosis and septal fibrosis. Biopsy is not necessary before hepatitis C treatment but may be helpful for decisions about the timing of treatment and surveillance for varices and hepatocellular carcinoma.

Diagnostic Tests

Antibody to HCV (anti-HCV) indicates either current infection or a previous infection with subsequent clearance. Even after clearance of the infection, anti-HCV is no longer detectable in only about 10% of patients. The diagnosis of hepatitis C infection is confirmed by the presence of HCV RNA in serum. Levels of HCV RNA do not correlate with either disease severity or prognosis; the main use of HCV RNA quantitation is to help stratify response to therapy. Patients with viral levels higher than 800,000 IU/mL are less likely to have a response to treatment than those with lower HCV RNA levels.

Identification of the HCV genotype is necessary to help determine the optimal treatment regimen. Liver biopsy is not necessary for the diagnosis of hepatitis C but may be helpful in assessing the severity of disease for making decisions about treatment and screening. Typical biopsy findings include a mononuclear (predominantly lymphocytic) portal hepatitis with lymphoid follicles

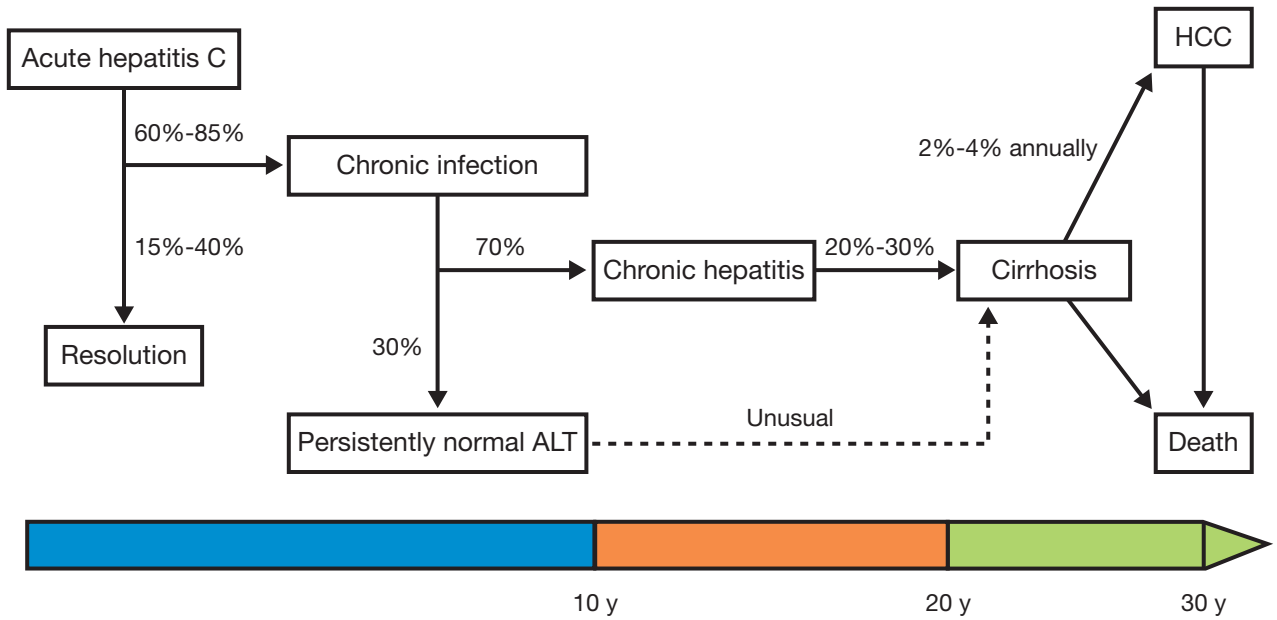

Figure 23.3. Natural History of Hepatitis C. Percentage values refer to patients. ALT indicates alanine aminotransferase; HCC, hepatocellular carcinoma.

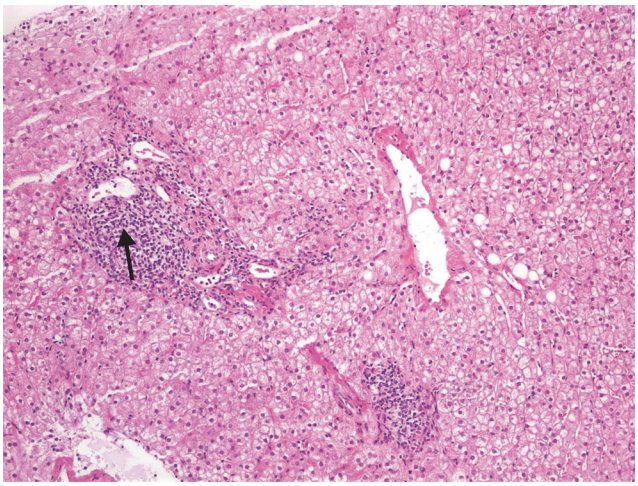

Figure 23.4. Biopsy Specimen From Patient With Hepatitis C. Note the portal infiltrate, lymphoid follicle (arrow), and mild steatosis.

and mild steatosis (Figure 23.4). Patients with risk factors for nonalcoholic fatty liver disease and those with HCV genotype 3 have more prominent steatosis than other HCV patients. Staging of fibrosis is often done with a 5-point scale, from 0 (no fibrosis) to 4 (cirrhosis).

Treatment

The treatment of hepatitis C has improved dramatically since 2013 but continues to evolve. Nomenclature used to define outcomes of hepatitis C treatment is shown in Table 23.7. Patients who respond to treatment and remain HCV RNA negative 24 weeks after completion of therapy (ie, they have a sustained virologic response [SVR]) are cured of hepatitis C infection and have improved outcomes compared with those who do not clear the virus. However, patients with cirrhosis remain at risk for hepatocellular carcinoma despite having an SVR, and continued monitoring is advised.

As mentioned above, treatment of hepatitis C continues to evolve. For patients infected with HCV genotype 1, treatment is currently with peginterferon; ribavirin; and simeprevir *or* sofosbuvir, sofosbuvir *and* ribavirin, or sofosbuvir *and* simeprevir. Additional oral agents are currently under review by the US Food and Drug Administration and will probably obviate the need for peginterferon in all or nearly all patients in the near future. Duration of treatment is now only 12 weeks with peginterferon, ribavirin, and sofosbuvir or sofosbuvir *and* simeprevir. Telaprevir and boceprevir are no longer used for the treatment of hepatitis C. Patients infected with HCV genotype 4 or 6 are currently treated similarly to patients with HCV genotype 1. Patients infected with HCV genotype 2 are treated with sofosbuvir and ribavirin for 12 weeks; patients infected with HCV genotype 3 are treated with the same regimen but for 24 weeks.

Patients who are not candidates for treatment should be evaluated annually with a complete blood cell count and liver blood tests. For those with early-stage disease, another liver biopsy in 3 to 5 years may be indicated to assess for histologic progression, although therapy should be reconsidered as new treatments become available. Magnetic resonance elastography and ultrasound-based transient elastography are not widely available but offer the potential for noninvasive serial measurements of fibrosis.

Patients with biopsy-proven or clinically apparent advanced fibrosis or cirrhosis are at increased risk for hepatocellular carcinoma. The risk of hepatocellular carcinoma complicating hepatitis C with cirrhosis is 1.4% to 4% per year. Screening using liver imaging, such as ultrasonography, computed tomography, or magnetic resonance imaging, every 6 to 12 months is advised for patients with cirrhosis who are candidates for treatment of hepatocellular carcinoma with liver transplant, liver resection, or percutaneous ablation.

Patients with hepatitis C and decompensated cirrhosis (including those with hepatocellular carcinoma) should be considered for liver transplant. Hepatitis C therapy for those with decompensated cirrhosis can now be considered because of the safety of interferon-free regimens.

Among patients who receive a liver transplant for hepatitis C, posttransplant viremia is nearly universal and histologic changes in the allograft due to recurrent disease are common. Nevertheless, the survival rate is good, and hepatitis C is the leading indication for liver transplant in the United States.

Patients with hepatitis C–associated cryoglobulinemia usually have a vasculitic rash on the lower extremities, but they also may have a membranoproliferative glomerulonephritis or polyneuropathy. Mild cryoglobulinemia and its associated complications usually respond to the treatment of hepatitis C; more severe disease may require immunosuppressive therapy, such as corticosteroids and rituximab. Porphyria cutanea tarda is manifested as a rash on sun-exposed areas, particularly the back of the hands. Most patients also have abnormal iron test results, and phlebotomy improves the rash of porphyria cutanea tarda. The response of porphyria cutanea tarda to hepatitis C therapy is more uncertain than the response of cryoglobulinemia.

Prevention

No vaccine is available for hepatitis C. Transmission by needlestick injury is unusual, although monitoring after inadvertent

Table 23.7. Hepatitis C Treatment Response Definitions

Virologic Response	*Definition*
End-of-treatment response	HCV RNA negative at end of treatment
Sustained virologic response	HCV RNA negative 24 wk after end of treatment
Breakthrough	Reappearance of HCV RNA during treatment
Relapse	End-of-treatment response without sustained response
Nonresponder	Failure to clear HCV RNA during treatment
Null responder	Usually used for peginterferon-ribavirin dual therapy; failure to decrease HCV RNA by week 12 of therapy
Partial responder	Usually used for peginterferon-ribavirin dual therapy; 2 $\log_{10}$ decrease in HCV RNA by week 12 of therapy, but still HCV RNA positive at 24 wk

Abbreviation: HCV, hepatitis C virus.
Adapted from Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74. Used with permission.

exposure is advised. Baseline anti-HCV testing is recommended with subsequent determination of the HCV RNA level 4 weeks after exposure. Antiviral therapy is more effective for acute hepatitis C than for chronic hepatitis C. For patients with documented acute hepatitis C, the current recommendation is 3 months of observation to allow for spontaneous resolution. If there is no spontaneous resolution, treatment is initiated.

Perinatal transmission of HCV occurs in about 5% of infants born to infected mothers. Rates are highest if the mother has high HCV RNA levels (eg, those coinfected with HCV and HIV). Maternally derived anti-HCV may be found in the neonate for up to 18 months after birth, thus limiting the usefulness of serologic assays for diagnosis; instead, HCV RNA testing should be used.

For patients infected with HCV, blood donation is prohibited. Precaution needs to be taken when caring for open sores of HCV-infected patients. Sexual transmission is unusual, but condoms are advised for those with multiple sex partners. For patients in a monogamous long-term relationship, the partner should be tested and the couple counseled about the possibility of transmission. The decision about the use of condoms is left to the infected person and partner.

Hepatitis E

Hepatitis E causes large outbreaks of acute hepatitis in underdeveloped countries. Recently, infection with a different strain of hepatitis E has been identified in more developed countries, including the United States. Clinically, hepatitis E virus infection is similar to HAV infection. Resolution of the hepatitis is the rule, and chronic infection does not occur. Women who acquire hepatitis E during pregnancy may present with fulminant liver failure.

Viral Hepatitis and HIV

Because of shared risk factors, patients with viral hepatitis are also at risk for infection with HIV. About 10% to 15% of HIV-infected patients are HBsAg positive. Compared with HIV-negative patients, patients with HIV infection are at increased risk for remaining chronically infected after the acute HBV infection. HIV-infected patients with HBV infection have higher HBV DNA levels and increased mortality from liver disease than HBV patients without HIV infection.

The response to treatment of HBV infection with peginterferon in HIV-infected patients is low, and treatment with oral agents generally is advised. The combination of tenofovir and emtricitabine has an antiviral effect on both HIV and HBV and is often used. For the rare patient who requires treatment of HBV but not HIV, lamivudine, entecavir, or tenofovir should not be given as monotherapy because of the risk of resistance developing to later treatment of HIV disease.

About 45% of HIV-infected patients are infected with HCV. Compared with HCV-infected patients without HIV infection, patients infected with both HCV and HIV have higher HCV RNA levels, an increased risk of vertical and sexual transmission of HCV, an increased risk of cirrhosis, and an increased risk of hepatocellular carcinoma. Patients infected with both HCV and HIV should be considered for treatment. The HIV disease should be controlled, and treatment generally is recommended only if the HIV level is less than 1,000 copies/mL and the CD4 cell count more than 200/mL.

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24

Clinical Approach to Liver Mass Lesions[a]

LEWIS R. ROBERTS, MB, ChB, PhD

The clinical approach to liver mass lesions requires attention to the clinical context within which the mass is identified, the symptoms of the patient, and the physical examination, laboratory tests, and imaging studies. With the advent of frequent ultrasonographic or cross-sectional imaging of the abdomen for various abdominal symptoms, many liver mass lesions are now discovered incidentally during imaging performed for unrelated symptoms. It is important to evaluate fully these incidentally discovered lesions because a significant proportion of them represent malignant or premalignant disease that requires appropriate management. This chapter describes the overall approach to the evaluation and diagnosis of liver mass lesions and summarizes the clinical features and management of the most common benign and malignant liver masses (Box 24.1).

[a] Portions previously published in Alberts SR, Gores GJ, Kim GP, Roberts LR, Kendrick ML, Rosen CB, et al. Treatment options for hepatobiliary and pancreatic cancer. Mayo Clin Proc. 2007 May;82(5):628-37. Used with permission of Mayo Foundation for Medical Education and Research.

Abbreviations: CA19-9, carbohydrate antigen 19-9; CRP, C-reactive protein; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PEI, percutaneous ethanol injection; PET, positron emission tomography; PTC, percutaneous transhepatic cholangiography; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization

Evaluation

History

It is important to obtain a history of potential risk factors for different types of liver masses to inform the subsequent evaluation and to limit unnecessary testing. The age and sex of the patient, a history of oral contraceptive use, geographic residence and travel history, and comorbid illnesses often provide important clues to the diagnosis. A history of previous imaging studies should always be sought because information about whether the mass is new, previously seen and stable in size, or enlarging over time can be very useful in the differential diagnosis of liver masses.

Pain can be an important presenting symptom. A rapidly enlarging liver mass tends to distend the liver capsule and cause right upper quadrant abdominal pain, whereas a slowly growing mass can reach a substantial size that almost completely occupies the liver without causing noticeable symptoms. The mass may come to attention only when it becomes a visible abdominal protuberance (Figure 24.1). Pain associated with tumor growth is usually dull, relatively diffuse, and persistent. It may or may not be associated with tenderness in the epigastrium and right upper quadrant of the abdomen. Subcapsular lesions, whether benign or malignant, frequently cause a pleuritic pain syndrome of abdominal pain accompanied by right shoulder discomfort exacerbated by breathing. In particular, lesions that have the propensity for intralesional rupture or hemorrhage can first become apparent with the sudden onset of severe abdominal pain. This is most typical of benign hepatic adenomas or hepatocellular carcinomas, which characteristically are extremely vascular. If

Box 24.1. Clinical Classification of Liver Mass Lesions

Benign lesions typically requiring no further treatment

- Cavernous hemangioma
- Focal nodular hyperplasia
- Simple liver cysts
- Focal fatty change or focal sparing in a fatty liver
- Angiolipoma

Benign lesions requiring further follow-up and management

- Hepatic adenoma
- Pyogenic liver abscess
- Nodular regenerative hyperplasia
- Biliary cystadenoma
- Inflammatory pseudotumor
- Granulomatous abscesses
- Amebic liver abscess
- Echinococcal cysts

Malignant lesions requiring appropriate therapy

- Liver metastases
- Primary hepatocellular carcinoma
- Cholangiocarcinoma
- Mixed hepatocellular-cholangiocarcinoma
- Cystadenocarcinoma
- Hemangioendotheliomatosis
- Epithelioid angiomyolipoma
- Mixed epithelial and stromal tumors
- Sarcomas

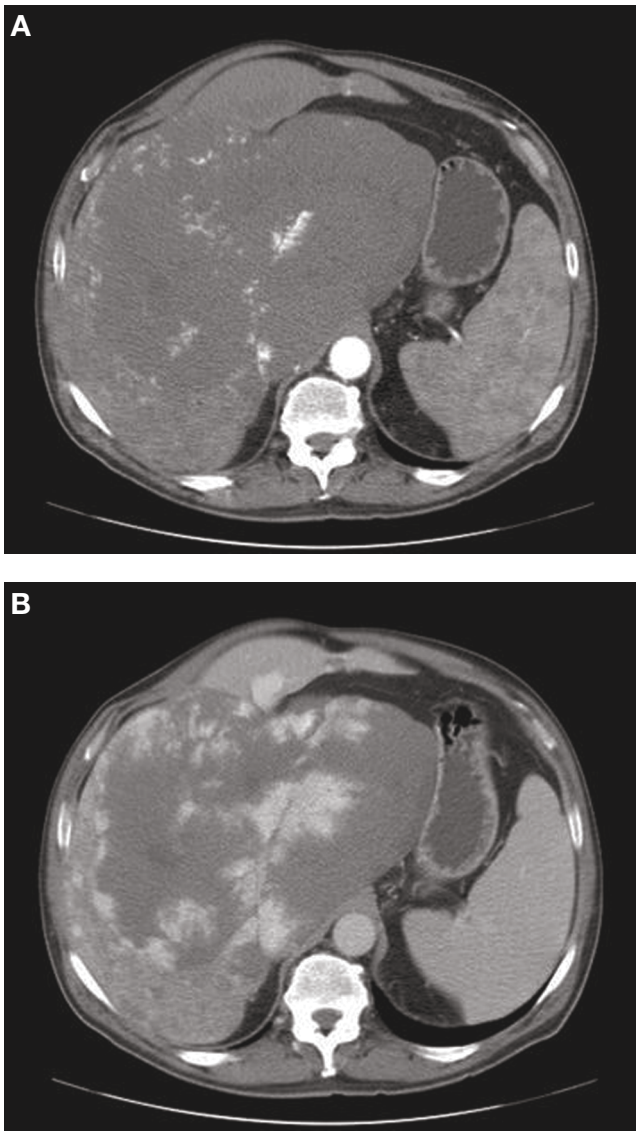

Figure 24.1. Large Cavernous Hemangioma With the Manifestation of an Abdominal Mass. A, Arterial phase shows peripheral nodular enhancement. B, Venous phase shows fill-in of contrast agent from the periphery toward the center of the mass.

the rupture involves the liver capsule, it can be associated with life-threatening intra-abdominal hemoperitoneum, shock, and risk of exsanguination.

A history of an underlying liver disease that predisposes to malignancy is often an important diagnostic clue. Patients with nonalcoholic steatohepatitis or viral, alcoholic, autoimmune, metabolic, or other causes of cirrhosis are at increased risk for hepatocellular carcinoma. These patients may have had complications of cirrhosis, including ascites, spontaneous bacterial peritonitis, bleeding esophageal varices, or hepatic encephalopathy. In addition, patients with long-standing chronic hepatitis B virus (HBV) infection are at risk for hepatocellular carcinoma even in the absence of cirrhosis. Consequently, current recommendations are for patients who have cirrhosis of any cause or who acquired chronic HBV infection at birth or in early life to begin a regular program of surveillance with ultrasonography of the liver, with or without measurement of serum alpha fetoprotein, every 6 months. Persons born in sub-Saharan Africa should be enrolled in a surveillance program beginning at age 20 years; for those born in Asia, surveillance should be initiated at age 40 years for men and 50 years for women (Figure 24.2). Regular surveillance should also be recommended for persons with a family history of hepatocellular carcinoma, those with high HBV viral loads (HBV DNA >2,000 IU/mL), and those with a persistent or intermittent increase in the level of alanine aminotransferase.

Primary sclerosing cholangitis, which can be subclinical in patients with ulcerative colitis or other inflammatory bowel disease, is a major risk factor for cholangiocarcinoma. A history of sudden hepatic decompensation, cholangitis, or the development of a new dominant stricture in a patient with known primary sclerosing cholangitis can presage the development of cholangiocarcinoma. More than half the cholangiocarcinomas that occur in patients with primary sclerosing cholangitis are diagnosed within 2 years after the initial diagnosis of primary sclerosing

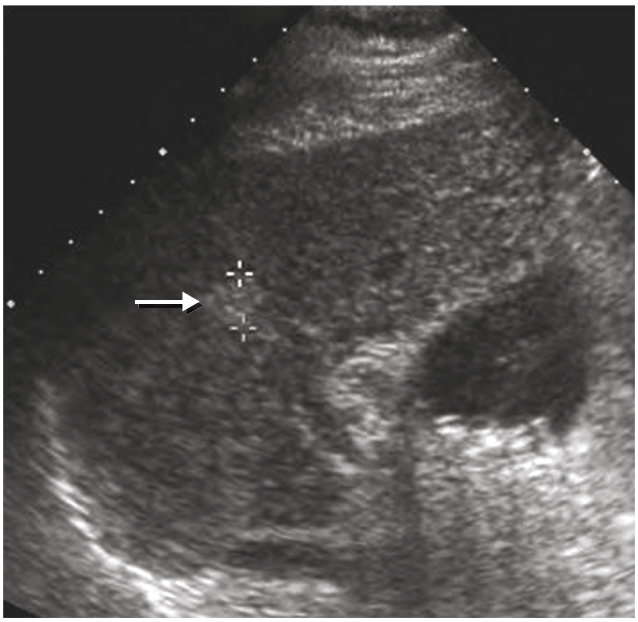

Figure 24.2. Surveillance Ultrasonography of the Liver. A small 1.3-cm mass (arrow) was identified in an at-risk patient during ultrasonographic screening for hepatocellular carcinoma.

cholangitis; therefore, this should be a period of heightened surveillance.

General, nonspecific symptoms associated with malignancy include fatigue, loss of appetite, unintended weight loss, low-grade fever, and night sweats. A recent history of iron deficiency anemia should raise suspicion of colorectal cancer with liver metastases; a long-standing history of gastroesophageal reflux and new-onset dysphagia should prompt consideration of esophageal adenocarcinoma; the recent onset of diabetes mellitus should elicit a search for pancreatic adenocarcinoma; and a history of breast cancer should be sought and the breasts should be examined and imaged to rule out metastatic breast cancer. In the absence of other localizing symptoms, occult lymphoma should be considered.

Various paraneoplastic syndromes can be helpful in the diagnosis of liver masses. A history of flushing, hypotension, and diarrhea is classic for metastatic neuroendocrine tumors such as carcinoids. Diarrhea alone occurs most frequently with hepatocellular carcinoma as a consequence of the secretion of vasoactive intestinal polypeptide and gastrin by the tumor. Also, hepatocellular carcinomas can be associated with hypoglycemia and erythrocytosis.

Physical Examination

The physical examination may provide clues to the underlying cause of a liver mass. Most frequently, patients have stigmata of chronic liver disease, including temporal muscle wasting, spider angiomas, palmar erythema, ascites, splenomegaly, and caput medusae from recanalization of the umbilical vein. The cirrhotic liver may be palpably nodular and often associated with bilobar enlargement of the liver or isolated hypertrophy of the caudate lobe. Large liver masses may give rise to palpable hepatomegaly, and subcapsular masses may be palpable if located anteriorly or inferiorly in the liver. Abdominal lymphadenopathy or peritoneal carcinomatosis may be palpable. Tumors may have associated tenderness in the epigastrium or right upper quadrant of the abdomen. Vascular masses such as primary hepatocellular carcinomas may have an audible vascular bruit on auscultation. Pallor may be due to anemia from colon adenocarcinoma with chronic blood loss, from portal hypertensive gastropathy in patients with cirrhosis, or from anemia of chronic disease related to other malignancies. Jaundice may be due to advanced chronic liver disease or to biliary obstruction from cholangiocarcinoma. Peripheral edema may be associated specifically with chronic liver disease or with tense ascites causing compression of the inferior vena cava and loss of intravascular oncotic pressure due to hypoalbuminemia, or it may be nonspecific from general debility. Frequently, cancer is associated with an acute phase response syndrome, and because albumin is a negative acute phase reactant, a cancer-associated hypoalbuminemia typically contributes to peripheral edema. Many cancers are associated with a prothrombotic tendency; consequently, it is important to evaluate new-onset lower extremity edema, particularly if it is unilateral, for deep vein thrombosis.

Laboratory Tests

Laboratory tests often provide evidence of chronic liver disease or of the underlying tumor that is metastatic to the liver. A complete blood cell count may show thrombocytopenia from chronic liver disease with splenomegaly, or it may show anemia from gastrointestinal blood loss related to colon or other primary gastrointestinal cancer. Typically, aspartate aminotransferase and alanine aminotransferase levels are increased from active inflammatory liver disease or from neoplastic diseases infiltrating the liver. An increase in the bilirubin and alkaline phosphatase concentrations usually reflects bile duct obstruction from a primary biliary tumor or it may be due to mass effect from an intrahepatic mass or from enlarged lymph nodes in the porta hepatis. The serum albumin level is often low and the prothrombin time increased in patients with cirrhosis.

Tests that identify the specific cause of liver disease, such as viral markers (anti-hepatitis C virus [HCV] antibody or polymerase chain reaction for HCV RNA), hepatitis B surface antigen, anti-HB core antibody, and anti-HB surface antibody, can be useful. Iron levels typically are increased in patients with hereditary hemochromatosis and low in those with anemia from colon cancer–related gastrointestinal blood loss. Tumor markers such as carcinoembryonic antigen for colon cancer, carbohydrate antigen 19-9 (CA19-9), and alpha fetoprotein are helpful if positive, but they frequently are negative in patients with early-stage cancer. Also, these markers are not entirely specific for the primary site. For example, the carcinoembryonic antigen level is often increased in cholangiocarcinomas and pancreatic cancers, and the alpha fetoprotein level can be increased in patients with primary cancers of the upper gastrointestinal tract outside the liver, such as esophageal adenocarcinoma. Primary hepatic lymphomas or secondary lymphoma metastases can masquerade as primary liver cancers; the serum level of lactate dehydrogenase usually is increased and can be an important clue to the diagnosis. The urine 24-hour 5-hydroxyindoleacetic acid concentration is helpful in cases of suspected carcinoid syndrome.

Imaging Studies

The imaging studies most frequently helpful in the differential diagnosis of liver mass lesions include abdominal ultrasonography, cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI),

positron emission tomography (PET), and fused PET-CT (most useful for imaging metastatic disease). More specialized contrast agents are becoming available, particularly for MRI. For example, gadoxetate disodium (Eovist) and gadobenate dimeglumine (MultiHance) both undergo biliary as well as renal excretion. These agents behave as nonspecific gadolinium chelates in the first minutes after administration and as liver-targeted agents in later delayed phases; this allows further delineation of lesion characteristics in MRI scans obtained 20 minutes (gadoxetate disodium) or 60 to 120 minutes (gadobenate dimeglumine) after injection of the contrast agent and can be particularly helpful for distinguishing between focal nodular hyperplasias and adenomas and for identifying small hepatocellular carcinoma nodules. The use of nuclear imaging studies, including tagged red blood cell studies (for cavernous hemangiomas), and technetium Tc 99m sulfur colloid imaging (to distinguish focal nodular hyperplasias from adenomas) has been largely replaced by the newer MRI contrast agents.

Benign Liver Masses

Cavernous Hemangioma

Cavernous hemangiomas are the most common benign liver tumors, occurring in 7% of adults in autopsy series. They are seen predominantly in women, with a female to male ratio ranging from 1.5:1 to 5:1; they are diagnosed most frequently in multiparous women in their third to fifth decades. Cavernous hemangiomas are multicentric in up to 30% of cases and frequently coexist with focal nodular hyperplasia.

Histologic Features

Cavernous hemangiomas are characterized by an extensive network of vascular spaces lined by endothelial cells and separated by thin, fibrous stroma. Large hemangiomas may have areas of thrombosis, scarring, and calcification.

Clinical Features

Patients with hemangiomas are most often asymptomatic. Large, subcapsular hemangiomas may cause abdominal pain or discomfort. Giant hemangiomas (>10 cm) may cause systemic features of inflammation such as fever, weight loss, and anemia. Kasabach-Merritt syndrome may occur with disseminated intravascular coagulation, most commonly in children. Cavernous hemangiomas do not undergo malignant transformation, and rupture is exceedingly rare.

Imaging Characteristics

Ultrasonography. On ultrasonography, hemangiomas are well circumscribed, homogeneously hyperechoic lesions with smooth margins.

Dynamic Contrast-Enhanced Multiphasic CT. On CT, there is peripheral nodular enhancement during the arterial phase, with later fill-in toward the center of the lesion (Figure 24.3).

MRI With Gadolinium Contrast. On contrast-enhanced MRI, hemangiomas are typically homogeneous, with low signal intensity on T1-weighted images and sharply demarcated, hyperintense lesions on T2-weighted images. Similar to other contrast imaging studies, there is peripheral enhancement in the arterial phase, with later fill-in toward the center of the lesion.

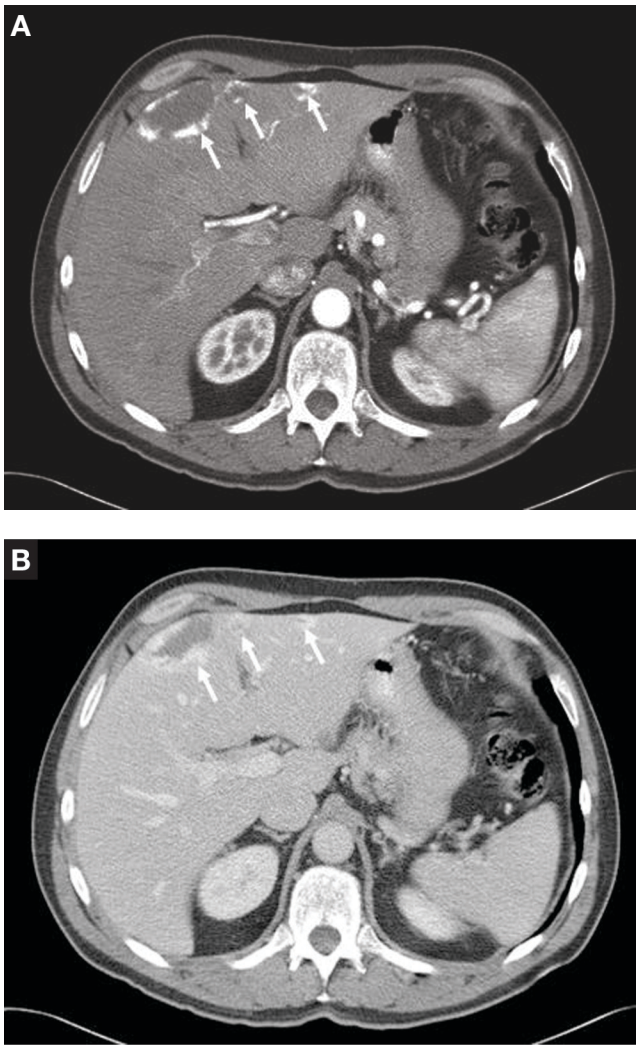

Figure 24.3. Cavernous Hemangioma on Computed Tomography. A, Arterial phase shows peripheral nodular enhancement of 1 large and 2 small cavernous hemangiomas (arrows). B, Venous phase shows fill-in toward the center of the 3 masses, with almost complete contrast enhancement of the 2 small hemangiomas (arrows).

Technetium Tc 99m–Labeled Red Blood Cell Scintigraphy. Scintigraphy can be used to confirm the diagnosis of lesions that are atypical on other imaging studies. There is low perfusion on early images, and the isotope gradually accumulates to a high concentration within the lesion on late images.

Biopsy

Biopsy seldom is needed. It may be useful for small lesions that show uniform enhancement and resemble primary tumors or metastases and also for large lesions that have pronounced scarring and atypical imaging features. Biopsy specimens are typically a relatively acellular "dry aspirate," with occasional vascular elements seen on histologic study.

Management

Most cavernous hemangiomas do not require intervention and can be observed. Symptomatic giant cavernous hemangiomas require surgical enucleation or resection.

Hepatic Adenoma

Hepatic adenomas are benign tumors of the liver that occur predominantly in young women between the third and fourth decades of life. Advances in molecular classification have identified hepatic adenomas as clonal tumors and led to the subclassification of adenomas into 4 molecular subgroups: 1) *HNF1A*-inactivated hepatocellular adenoma; 2) telangiectatic or inflammatory hepatocellular adenoma characterized by activating mutations of the interleukin 6 signal transducer (*IL6ST*), the guanine nucleotide-binding protein alpha stimulatory subunit complex locus (*GNAS*), or the signal transducer and activator of transcription 3 (*STAT3*) gene; 3) β-catenin–activated hepatocellular adenomas, which encompass both noninflammatory and inflammatory subgroups; and 4) unclassified hepatocellular adenoma.

Hepatic adenomas have been associated significantly with long-term use of oral contraceptive pills. In the era when oral contraceptives had relatively high doses of estrogens, studies estimated a relative risk of 2.5 times greater for women who had taken oral contraceptive pills for 3 to 5 years compared with women who had taken them for 1 year or less. After 5 years of oral contraceptive use, the risk increased sharply, reaching 25 times greater after 9 or more years of use. The epidemiology of hepatic adenomas is changing. Newer oral contraceptives contain lower amounts of estrogen and are probably associated with a lower risk of hepatic adenomas; however, the overall incidence of hepatic adenomas does not appear to have decreased concurrently.

With increasing rates of obesity worldwide, the prevalence of obesity and the metabolic syndrome are high among patients with hepatic adenomas, particularly the inflammatory or telangiectatic variant, suggesting that obesity and the metabolic syndrome increase the risk of adenomas. Further, obese patients are more likely to have multiple adenomas and to have progressive growth of adenomas if they do not lose weight. Excessive alcohol use has been associated with the development of inflammatory hepatocellular adenomas. Hepatic adenomas also occur in a familial pattern associated with the variety of type 2 diabetes mellitus known as maturity-onset diabetes of the young type 3, which is associated with germline mutations in the *HNF1A* gene; in patients with glycogen storage disease type 1A or 3; and in persons who take the androgenic hormones methandrostenolone and methyltestosterone.

Adenomas are usually single, but they may be multiple, especially in patients with maturity-onset diabetes of the young type 3 or glycogen storage disease. The tumors may decrease in size after withdrawal of oral contraceptives, but they usually do not; sometimes they increase in size. An important feature of hepatic adenomas is that they can undergo malignant transformation, although this seems to be relatively uncommon. Male sex, size greater than 5 cm, and β-catenin activation as assessed by increased nuclear β-catenin staining are the major risk factors for transformation to hepatocellular carcinoma.

Histologic Features

Adenomas are characterized by the presence of sheets of hepatocytes supplied by "naked" arteries (ie, arteries unaccompanied by bile ductules, fibrous septa, portal tracts, or central veins).

Clinical Features

Patients with hepatic adenomas are most often asymptomatic. However, they may present with pain or discomfort of the upper abdomen or the right upper quadrant of the abdomen. Because these tumors have a propensity to rupture, patients may present with intrahepatic hemorrhage and pain or with hemoperitoneum and shock.

Imaging Characteristics

Adenomas frequently have nonspecific imaging characteristics. Most often, they are heterogeneous because of the presence of intralesional necrosis or hemorrhage, but frequently they are homogeneous when small. The tumors typically take up the contrast agent rapidly in the arterial phase of contrast CT or MRI studies and then almost immediately become isointense with the surrounding liver in the early portal phase. If contrast studies are not optimally timed, this important imaging feature may be missed. Adenomas often cannot be differentiated definitively from hepatocellular carcinoma or hypervascular metastases with ultrasonography, CT, or MRI. On technetium Tc 99m sulfur colloid scintigraphy, there usually is no uptake because adenomas do not contain Kupffer cells. Adenomas can be differentiated from focal nodular hyperplasias in the delayed phase after MRI with gadobenate dimeglumine or gadoxetate disodium, in which adenomas show decreased retention of the contrast when compared with the surrounding liver (Figure 24.4).

Biopsy

Because of the frequent uncertainty about the diagnosis after a thorough noninvasive evaluation, biopsy often is required for diagnosis. Biopsy is also helpful for immunohistochemical and molecular classification to assess the risk of malignant transformation. *HMF1A*-incativated hepatocellular ademonas show loss of staining for liver fatty acid binding protein; inflammatory hepatocellular adenomas show uniform expression of serum amyloid A protein or C-reactive protein (CRP); and β-catenin–activated adenomas show uniform immunohistochemical staining for glutamine synthetase and nuclear staining for β-catenin, which is sometimes focal.

Management

Because of the risks of rupture or transformation to hepatocellular carcinoma, surgical resection is recommended for large hepatic adenomas (>5 cm), for hepatic adenomas of any size occurring in men, for hepatic adenomas with β-catenin activation, and for hepatic adenomas that are histologically difficult to distinguish from well-differentiated hepatocellular carcinomas.

Patients generally are advised to discontinue the use of oral contraceptive pills. If the adenoma is larger than 5 cm, most experts advise against pregnancy until the lesion can be resected, although the evidence that pregnancy is associated with a higher rate of complications is scant. Pregnancy in patients with smaller adenomas can be managed by careful observation with intermittent ultrasonography. Small adenomas located in the liver where they are technically difficult to resect can be treated with radiofrequency ablation. Observation is recommended for smaller adenomas or for those that regress after withdrawal of estrogen, particularly in patients who do not plan any future pregnancies.

Focal Nodular Hyperplasia

Focal nodular hyperplasia is thought to develop as a reaction of the liver to an intrahepatic arterial malformation. The arterial malformation forms a vascular stellate scar that contains connective tissue and bile ductules. The surrounding mass contains a proliferation of hepatocytes separated by fibrous septa. Unlike

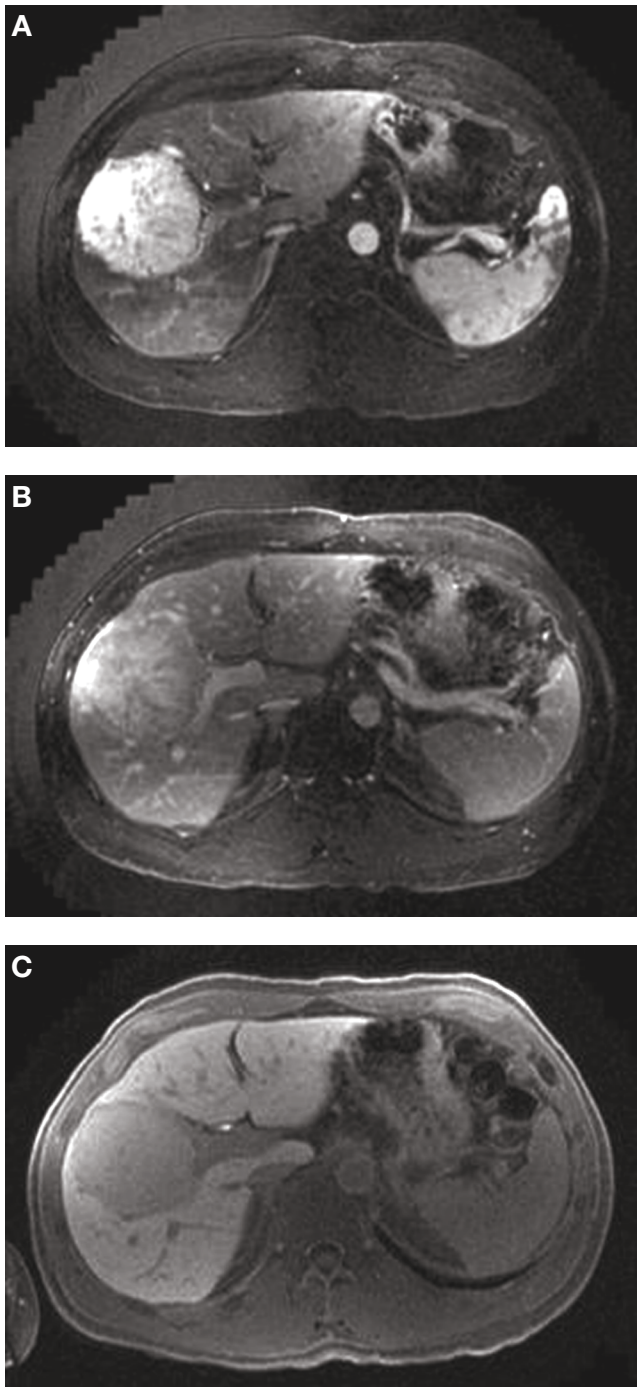

Figure 24.4. Hepatic Adenoma. A, Arterial phase after intravenous injection of gadobenate dimeglumine shows heterogeneous hyperenhancement. B, Venous phase shows the adenoma almost isoenhancing with the surrounding liver. C, Delayed hepatobiliary phase shows the adenoma excluding the contrast agent and hypoenhancing compared with the surrounding liver.

hepatic adenomas, focal nodular hyperplasias are polyclonal and do not have a tendency for malignant transformation. Focal nodular hyperplasia occurs predominantly in women of childbearing age. The relationship to oral contraceptive use is controversial, but some studies have suggested an association with long-term use. The tumor may be multiple (10% of patients) or associated with cavernous hemangiomas (20% of patients).

Histologic Features

Focal nodular hyperplasia is characterized by benign-appearing hepatic parenchyma, with bile ductules in septal fibrosis.

Clinical Features

Most patients with focal nodular hyperplasia are asymptomatic. Patients with large lesions may present with abdominal discomfort or an abdominal mass.

Imaging Characteristics

Ultrasonography. Focal nodular hyperplasia has a variable ultrasonographic appearance, with lesions being hypoechoic, hyperechoic, or isoechoic. Most commonly, the tumors are hypoechoic except for the central scar. Color flow Doppler imaging may show increased blood flow in the central stellate scar.

Multiphasic CT. On multiphasic CT, the presence of an avascular central scar or a feeding artery to the mass is highly suggestive of focal nodular hyperplasia. The lesion shows rapid and intense contrast enhancement during the arterial phase and isointensity during the venous phase.

Contrast-Enhanced MRI. Contrast-enhanced MRI shows a rapid, intense contrast enhancement similar to the pattern with multiphasic CT. Typically, focal nodular hyperplasia is isointense on T1-weighted images and either isointense or slightly hyperintense on T2-weighted images. The central scar is usually hypointense on T1-weighted images but hyperintense on T2-weighted images. Gadobenate dimeglumine or gadoxetate disodium is taken up by the hepatocytes and partially excreted into the immature bile ductules of the tumor (Figure 24.5).

Technetium Tc 99m Sulfur Colloid Scintigraphy. With scintigraphy, 50% to 60% of cases of focal nodular hyperplasia show hyperintense or isointense uptake, unlike the hypointensity of adenomas, because of the presence of Kupffer cells.

Biopsy

Focal nodular hyperplasia can be difficult to distinguish from adenoma because fine-needle aspirates from both lesions may show only benign-appearing hepatocytes. Immunohistochemically, focal nodular hyperplasia typically shows a patchy "map-like" glutamine synthetase staining, which distinguishes it from hepatic adenoma.

Management

Asymptomatic focal nodular hyperplasia can be monitored over time, and surgery rarely is indicated. Some groups recommend discontinuation of oral contraceptives, although this has not been shown to result in regression of the tumor.

Simple Liver Cysts

Solitary or multiple liver cysts are common and usually asymptomatic, and they often coexist with other mass lesions in the liver. The female to male ratio is 4:1. Liver cysts occur in 3.6% of the population, and the prevalence increases with age.

Histologic Features

Cysts are thin-walled structures lined by cuboidal bile duct epithelium and filled with isotonic fluid.

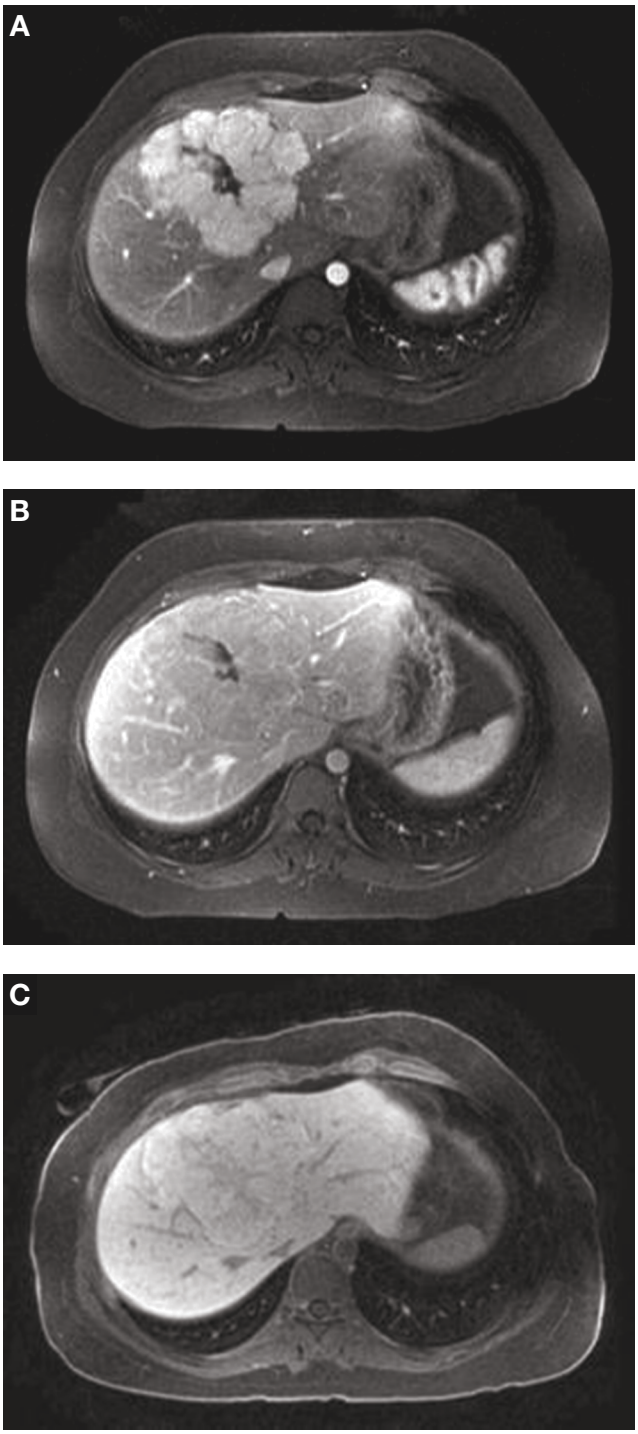

Figure 24.5. Focal Nodular Hyperplasia. A, Arterial phase shows homogeneous hyperenhancement and a central scar. B, Venous phase shows the tumor isoenhancing with the surrounding liver. C, Delayed phase after intravenous injection of gadobenate dimeglumine shows the contrast agent concentrated within the tumor.

Clinical Features

Cysts are usually asymptomatic unless they are large and causing symptoms through pressure on adjacent structures. Rarely, large cysts may cause biliary obstruction.

Imaging Characteristics

Ultrasonography. Ultrasonography is the best imaging method for cysts. Classically, cysts are anechoic and have smooth, round margins; a distinct far wall; and posterior acoustic enhancement (Figure 24.6). Ultrasonography clearly shows the wall thickness and internal septations, if present. Thick-walled cysts with nodularity or irregular septations suggest the diagnosis of cystadenoma or, rarely, cystadenocarcinoma.

Computed Tomography. On CT, cysts have the same density as water and do not change with contrast imaging.

Magnetic Resonance Imaging. On MRI, cysts are hyperintense in T2-weighted images. Small cysts may be difficult to differentiate from a cavernous hemangioma.

Biopsy

Biopsy usually is not necessary because of the distinctive imaging characteristics of simple cysts.

Management

Large symptomatic cysts can be treated with surgical fenestration or percutaneous aspiration and instillation of ethanol to ablate the cyst.

Focal Fat or Fat Sparing

Fatty infiltration of the liver is common. Focal fatty infiltration can give the appearance of a mass lesion on imaging studies; conversely, focal sparing in a liver with diffuse fatty infiltration also can have the appearance of a mass. Fatty infiltration typically occurs in obese persons and in patients with diabetes mellitus, high alcohol consumption, or altered nutritional status because of chemotherapy regimens.

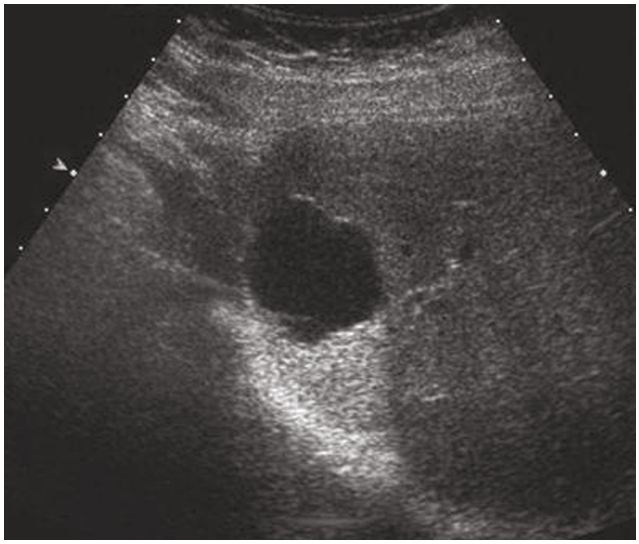

Figure 24.6. Simple Liver Cyst. Ultrasonogram shows the characteristic changes of absence of echoes within the lesion, a distinct far wall, and increased echogenicity posterior to the cyst.

Histologic Features

Histologic specimens show areas of fatty infiltration with fat-laden cells.

Clinical Features

Focal fat or fat sparing is asymptomatic and usually discovered on abdominal imaging performed for other reasons.

Imaging Characteristics

Focal fat does not distort the contour of the liver. If normal vessels, especially veins, can be seen coursing through the region, the diagnosis of focal fat is likely. Also, focal fat typically occurs in vascular watersheds, particularly along the falciform ligament. "Skip areas" of normal liver in diffuse fatty infiltration typically occur adjacent to the gallbladder fossa, in subcapsular areas, or in the posterior aspect of segment 4 of the liver.

Ultrasonography. Areas of fatty infiltration are hyperechoic.

Computed Tomography. On CT, fat is hypodense compared with the spleen, but because the fat is dispersed in normal tissue, it is not as low in density as adipose tissue. Venous structures coursing through the areas of focal fat are seen on venous phase studies.

Magnetic Resonance Imaging. On MRI, fat is occasionally hyperintense on T1- and T2-weighted images. Decreased signal intensity on out-of-phase gradient imaging is diagnostic of focal fat.

Biopsy

Biopsy can be used to exclude other lesions if the diagnosis cannot be established confidently.

Management

No therapy is needed. Areas of focal fat may resolve if patients lose weight or achieve better control of diabetes.

Malignant Liver Masses

Hepatocellular Carcinoma

The major risk factors for hepatocellular carcinoma include cirrhosis from chronic HBV or HCV infection, alcohol use, hereditary hemochromatosis, and other causes of liver injury such as alpha$_1$-antitrypsin deficiency, autoimmune hepatitis, primary biliary cirrhosis, and tyrosinema. Fungal aflatoxins that contaminate grains and legumes also have a synergistic effect with other causes of liver injury and contribute to the development of liver cancer in parts of sub-Saharan Africa and Asia. Approximately 80% to 90% of hepatocellular carcinomas occur with cirrhosis. The other 10% to 20% comprise 2 groups. One group includes patients who have chronic HBV infection and hepatocellular carcinoma in the absence of cirrhosis, presumably because of the oncogenic effects of HBV proteins and HBV integration, inherited familial tendency, and, in certain areas of the world, the synergistic effect of exposure to dietary aflatoxin. These patients are often young, between 20 and 50 years old. The second group of noncirrhotic patients is characterized by older persons who live in countries where the incidence of HBV infection is low and who present with sporadic hepatocellular carcinoma in the absence of discernible risk factors. Without surveillance, most hepatocellular carcinomas are diagnosed at an advanced stage, when radical treatment for cure is no longer feasible. Therefore, it is important that persons who are at risk for hepatocellular carcinoma be enrolled in a surveillance program for early detection of new tumors.

Surveillance and Diagnosis With Imaging or Biopsy

The best outcomes for treatment of hepatocellular carcinoma are achieved with liver transplant, surgical resection, or local ablative therapies such as radiofrequency ablation, laser ablation, microwave ablation, or percutaneous ethanol injection. Because these therapies are most effective when applied to early-stage hepatocellular carcinoma, there is a strong rationale for emphasizing a regular surveillance program to screen for the tumor in at-risk persons. Current guidelines recommend that patients who have cirrhosis be evaluated with liver ultrasonography every 6 months to screen for hepatocellular carcinoma. For those who have chronic hepatitis B without cirrhosis, screening should begin at age 20 years for Africans, 40 years for Asian men, and 50 years for Asian women or for patients with a family history of hepatocellular carcinoma, high HBV DNA, and a persistent or intermittent increase in the level of alanine aminotransferase. The serum level of alpha fetoprotein has low sensitivity for the detection of early-stage hepatocellular carcinoma, and its use is controversial. Current guidelines of the American Association for the Study of Liver Diseases do not recommend the use of alpha fetoprotein for surveillance except when high-quality ultrasonography is not available. However, the high body mass index and central obesity of many US patients frequently render full ultrasonographic visualization of the liver difficult; hence, alpha fetoprotein measurement remains part of the de facto standard for surveillance of hepatocellular carcinoma.

Once a new mass is identified with ultrasonography, it should be confirmed with cross-sectional imaging with multiphasic contrast-enhanced CT or MRI. The combination of arterial enhancement with washout in the portal venous phase is the hallmark of early-stage hepatocellular carcinoma and is highly specific (Figure 24.7). Hepatocellular carcinoma can be diagnosed noninvasively if a new nodule larger than 1 cm is found in a cirrhotic liver during surveillance and shows typical arterial enhancement and venous washout on triphasic CT or MRI. Additional MRI features of hepatocellular carcinoma include contrast exclusion in the delayed biliary phase of imaging with gadoxetate disodium and hyperintensity on diffusion-weighted imaging. The main rationale for noninvasive diagnosis in early-stage hepatocellular carcinoma is to prevent tumor seeding and recurrence after potentially curative treatment, including liver transplant. Patients who present with newly discovered liver masses in the absence of cirrhosis should have a biopsy study to histologically confirm hepatocellular carcinoma because conditions such as lymphomas and metastases from other primary sites not infrequently masquerade as hepatocellular carcinoma in a noncirrhotic liver. Determination of the alpha fetoprotein level may obviate the need for biopsy if the level is markedly increased, but it is important to consider that malignancies at other primary sites, notably esophageal and gastric carcinomas, also can be associated with a high level of alpha fetoprotein.

Management

Liver Transplant. Liver resection and transplant offer the greatest chance of cure for patients with hepatocellular carcinoma. The decision to choose resection or transplant is based on a careful

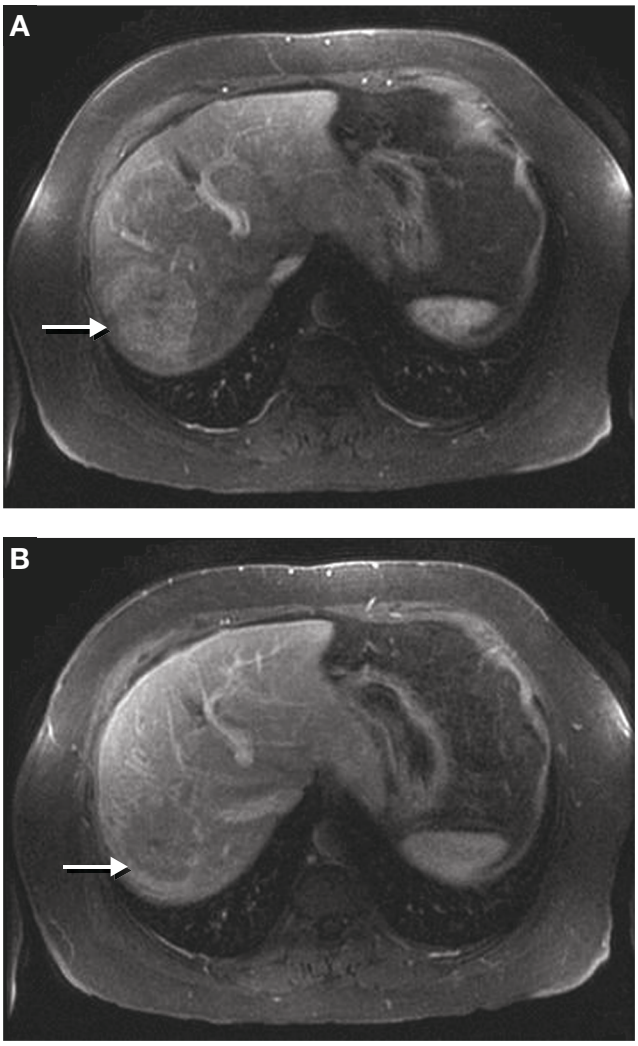

Figure 24.7. Hepatocellular Carcinoma. A, Arterial phase shows vascular enhancement (arrow). B, Portal phase shows venous washout (arrow).

evaluation of the comorbid conditions of the patient, liver function, tumor size, number of tumors, vascular invasion, candidacy for transplant, and organ availability. Transplant is an effective treatment option for hepatocellular carcinoma in patients with cirrhosis because it addresses both the neoplasm and the underlying liver disease. Initially, the outcomes of transplant for hepatocellular carcinoma were poor. However, with advances in patient selection using the Milan criteria (1 tumor ≤5 cm or 2 or 3 tumors ≤3 cm, without vascular invasion or extrahepatic spread), the 5-year survival rate is 70% to 80% and the recurrence rate is less than 15%. Despite the favorable results of transplant, organ availability is less than the demand, and up to 15% of patients listed for transplant drop out because of tumor progression before an organ becomes available.

Surgery. Liver resection is the preferred treatment of hepatocellular carcinoma in patients without cirrhosis and in those with cirrhosis who have well-preserved liver function and little or no portal hypertension. For patients without cirrhosis, major liver resection carries a low mortality rate (<5%) and a 5-year survival rate of 30% to 50%. Bleeding and liver failure are the major causes of perioperative mortality among patients with cirrhosis who undergo liver resection. Limited liver resections are safe in patients with cirrhosis who have preserved liver function (Child-Pugh class A) and no portal hypertension. Multiple methods of assessing liver function, liver reserve, and perioperative mortality have been described and are important in selecting patients for resection. The Model for End-stage Liver Disease (MELD) has been shown to predict perioperative mortality after liver resection. Patients with a MELD score less than 9 have a perioperative mortality rate of 0%, compared with 29% for those with a score of 9 or more. After liver resection, the tumor recurs in approximately 70% of patients within 5 years and reflects both intrahepatic metastases and the development of de novo tumors in the diseased liver. Predictors of recurrence and survival after resection include tumor size and number and vascular invasion. The 5-year survival rate after liver resection is 30% to 50%. For ideal candidates (ie, they have a single tumor, preserved liver function, and absence of portal hypertension), the 5-year survival rate is as high as 50% to 70%.

Local and Locoregional Therapies. Local therapies for treating hepatocellular carcinoma include ablative methods such as radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI). RFA is the more effective ablative treatment and is used more often than PEI in clinical practice. It has the same efficacy as surgical resection in treating single, small (<2 cm) hepatocellular carcinomas. RFA is generally used for treatment of small hepatocellular carcinomas (≤3 cm) in patients who are not candidates for liver transplant or when liver transplant is not available. With RFA, a high-frequency electrical current is applied to a treatment probe that is inserted into the tumor. RFA typically produces complete necrosis of a 3- to 4-cm radius of tissue during a single 10- to 15-minute treatment. RFA can be applied to overlapping fields to treat lesions larger than 3 cm, but it is not as effective for these lesions. RFA is not effective for the treatment of tumors close to major blood vessels because a heat-sink effect causes rapid conduction of heat away from the tumor. Also, RFA can damage the biliary tree if applied too close to major bile ducts. Several early studies raised concerns about increased risks of tumor seeding after RFA. Advances in the ablation technique have lowered this risk substantially. Most often, surface lesions are approached through the liver parenchyma rather than through direct puncture of the liver surface. In addition, the probe track is cauterized as the probe is being removed; this destroys and prevents dissemination of any residual hepatocellular carcinoma cells.

PEI is performed under ultrasonographic guidance. Ethanol induces tumor necrosis and is particularly effective in the cirrhotic liver because the surrounding fibrotic tissue limits the diffusion of the injected ethanol. Usually 2 or 3 injection sessions are needed for complete ablation of the tumor. The low cost of this treatment makes it attractive for use in lower income countries.

Alternative means of local ablation that are being used more frequently include laser ablation, microwave ablation, and irreversible electroporation.

Locoregional therapies include transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and conformal beam radiotherapy. TACE involves the angiographic injection of a combination of chemotherapy agents with absorbable gelatin sponge particles into the branch of the hepatic artery that supplies the tumor. The goal is to deliver high concentrations of antitumor agents and, simultaneously, to induce tumor necrosis by occluding the arterial supply to the tumor. The chemotherapy agents typically used for TACE include cisplatin, doxorubicin,

and mitomycin C. Some centers use chemotherapy agents dissolved in iodized oil (Lipiodol); however, this iodinated contrast agent can interfere with subsequent detection of arterial enhancement in residual tumor nodules. TACE is particularly effective in the treatment of hepatocellular carcinoma because almost all the blood supply to the tumor is from branches of the hepatic artery. In contrast, the nontumoral liver has a dual blood supply, with 70% to 80% of the blood supply provided by the portal vein and 20% to 30% by the hepatic artery. Consequently, occlusion of the branches of the hepatic artery to the tumor can be achieved without substantially compromising the blood supply to the surrounding cirrhotic liver. The major contraindication to TACE is complete obstruction of the portal vein, in which case concomitant obstruction of the arterial supply can lead to hepatic ischemia and induce liver decompensation. Randomized controlled trials have shown that TACE improves survival of patients with unresectable intermediate-stage hepatocellular carcinoma. TACE is an alternative treatment option for patients with early-stage hepatocellular carcinoma when ablative treatment cannot be performed safely because of the location of the tumor. TACE also is used frequently for downsizing the tumor or as a bridging treatment before liver transplant.

Drug-eluting bead TACE uses porous drug-eluting beads loaded with doxorubicin for chemoembolization. The beads lodge in the tumor capillaries and gradually release doxorubicin into the local environment. Theoretically, treatment of intrahepatic tumors with drug-eluting bead TACE is more sustained and causes fewer systemic side effects. Most studies suggest that its efficacy is similar to that of conventional TACE.

TARE delivers intratumoral radiation by transarterial injection of yttrium-90 radioactive microspheres, following the principles of TACE. Increasingly, TARE has been used for patients with unresectable multifocal hepatocellular carcinoma, including hepatocellular carcinoma with portal vein invasion. Although TARE has not been studied as rigorously as TACE, it appears to result in clinical outcomes equivalent to those of TACE, with acceptable safety and improved tolerability.

Systemic or Targeted Therapy. In early 2007, a large multicenter study showed that the multitargeting kinase inhibitor sorafenib had significant efficacy in a population of patients, most of whom were in Child-Pugh class A, who had advanced unresectable hepatocellular carcinoma. Among these patients, the median time to radiographic progression doubled from 12.3 to 24.0 weeks and overall survival increased from 34.4 to 46.3 weeks. Sorafenib was approved by the US Food and Drug Administration in late 2007 for treatment of unresectable hepatocellular carcinoma and is the current standard of care for advanced hepatocellular carcinoma.

Cholangiocarcinoma

Cholangiocarcinomas are malignancies that arise from the bile duct epithelium. In Western countries, primary sclerosing cholangitis is the primary identified risk factor for cholangiocarcinoma. In several countries in Asia, liver fluke infestations of the biliary tract are an important risk factor. Choledochal and other cystic disorders of the biliary tract also are associated with cholangiocarcinoma. Patients with chronic HCV infection with cirrhosis are also at increased risk for cholangiocarcinoma. However, most patients with cholangiocarcinoma have no known risk factors. For patients with primary sclerosing cholangitis, the risk of diagnosis of cholangiocarcinoma is highest within the first 2 years after the diagnosis of primary sclerosing cholangitis, suggesting perhaps that the development of cancer is the event that in some way triggers the diagnosis of primary sclerosing cholangitis.

Cholangiocarcinomas are classified as intrahepatic or extrahepatic tumors. The manifestation of intrahepatic cholangiocarcinomas is typically a large intrahepatic mass with or without intrahepatic or regional lymph node metastases. Extrahepatic cholangiocarcinomas may be perihilar tumors, which arise in the distal right or left hepatic duct or at the common hepatic duct bifurcation, or distal bile duct tumors arising in the common bile duct. The laboratory test most often used to confirm the diagnosis of cholangiocarcinoma is measurement of the CA19-9 level. A CA19-9 value greater than 100 U/mL is about 65% to 75% sensitive and 85% to 95% specific for the diagnosis of cholangiocarcinoma. CA19-9 also can be increased in pancreatic adenocarcinomas and other upper gastrointestinal tract malignancies. CA19-9 values greater than 1,000 U/mL usually are predictive of extrahepatic metastatic disease.

Histologic Features

Histologically, cholangiocarcinomas are adenocarcinomas. This frequently leads to confusion about the primary site of the tumor. Thus, cholangiocarcinoma can be misdiagnosed as metastatic adenocarcinoma of unknown primary site.

Clinical Features

The clinical features of cholangiocarcinoma depend on its location. Approximately 60% to 70% of these tumors are at the bifurcation of the hepatic duct; the rest occur in the extrahepatic (20%-30%) or intrahepatic (5%-15%) biliary tree. The most common symptom of extrahepatic cholangiocarcinoma is painless jaundice due to obstruction of biliary ducts. With tumors of the intrahepatic bile ducts, patients often have pain without jaundice. With perihilar or intrahepatic tumors, jaundice often occurs later in the disease course and is a marker of advanced disease. Other common symptoms include generalized itching, abdominal pain, weight loss, and fever. Pruritis usually is preceded by jaundice, but it may be the initial presenting symptom of cholangiocarcinoma. The pain associated with cholangiocarcinoma is usually a constant dull ache in the right upper quadrant of the abdomen. Biliary obstruction results in clay-colored stools and dark urine. Physical signs include jaundice, hepatomegaly, and a palpable right upper quadrant mass. Patients with intrahepatic cholangiocarcinoma most often present with dull right upper quadrant discomfort and weight loss.

Imaging Characteristics

Abdominal Ultrasonography. Cholangiocarcinomas are typically hypoechoic on ultrasonography and sometimes are first visualized during an ultrasonographic examination of the liver for suspected gallstone disease causing right upper quadrant abdominal discomfort.

Multiphasic CT. Intrahepatic cholangiocarcinomas are usually hypodense on noncontrast imaging, often with a rounded, smooth, nodular appearance. During the arterial phase, there is minimal enhancement that progressively increases through the venous phase, often more prominent peripherally than centrally. Perihilar cholangiocarcinomas that preferentially affect 1 lobe of the liver often lead to unilobar biliary obstruction for an extended period, during which the patient has a normal bilirubin level because of adequate biliary drainage from the unaffected

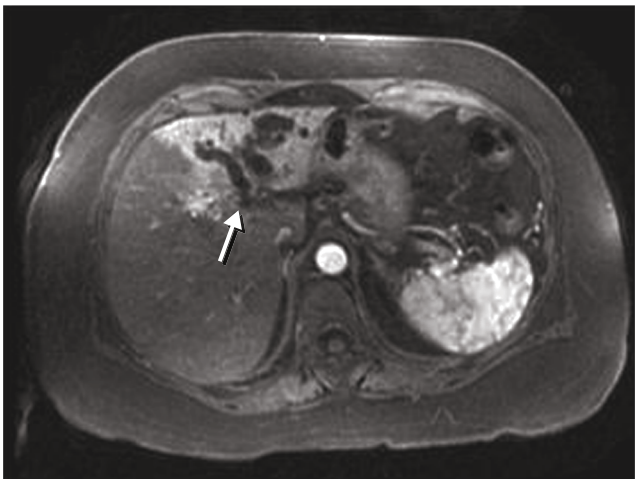

Figure 24.8. Cholangiocarcinoma With Atrophy-Hypertrophy Complex. Note cholangiocarcinoma with obstruction of the left biliary ductal system (arrow) and consequent marked dilatation of the bile ducts in the left lobe, with associated atrophy of the left lobe parenchyma. The right lobe shows compensatory hypertrophy.

lobe of the liver. Eventually, the affected lobe undergoes atrophy, with prominent biliary dilatation, while the unaffected lobe undergoes compensatory hypertrophy. This syndrome is called the atrophy-hypertrophy complex (Figure 24.8). Cross-sectional imaging is particularly helpful for assessing the degree of encasement of the hilar vasculature, a critically important part of the evaluation for surgical resectability.

MRI With Gadolinium or Ferumoxides. With contrast-enhanced MRI, intrahepatic cholangiocarcinomas are hypointense on T1-weighted images and hyperintense on T2-weighted images. There is peripheral contrast enhancement that progresses into the venous phase, similar to the pattern seen with multiphasic CT. Imaging with ferumoxides can enhance visualization of small peribiliary cholangiocarcinomas. Magnetic resonance cholangiopancreatography (MRCP) is performed concomitantly with MRI and is now recommended as the optimal initial investigation for assessing the luminal extent and resectability of suspected cholangiocarcinoma. MRCP is noninvasive and as accurate as direct cholangiography for assessing the level of biliary tract obstruction. Often, the biliary tract peripheral to a biliary stenosis can be demonstrated better with MRCP than with endoscopic retrograde cholangiopancreatography (ERCP).

Cholangiography. With the advent of MRI and MRCP, direct cholangiography by means of ERCP and percutaneous transhepatic cholangiography (PTC) are becoming less important as initial diagnostic methods; however, the resolution provided by PTC and ERCP is still better in some cases than that of MRCP. In addition to providing tissue samples by brush cytology or biopsy, PTC and ERCP allow placement of therapeutic stents for biliary decompression if needed and also can be used to deliver photodynamic therapy to unresectable tumors. In patients with primary sclerosing cholangitis, PTC may be challenging technically because of peripheral strictures; for these patients, ERCP is the preferred method. A completely occluded distal biliary tract may preclude the use of ERCP, and either PTC or a combined approach of PTC and ERCP may be needed for successful passage through a difficult stricture to accomplish internal biliary drainage, which is preferred to external drainage.

Biopsy and Cytology

Intrahepatic mass-forming cholangiocarcinomas usually are biopsied under ultrasonographic or CT guidance. Often, ductal cholangiocarcinomas are less amenable to percutaneous needle biopsy. Also, autoimmune pancreatitis with biliary involvement can mimic a malignant biliary stricture, rendering the accurate diagnosis of biliary strictures even more difficult. Pinch forceps biopsies and cytologic brushings usually are obtained at ERCP or PTC to help establish the diagnosis. Because many cholangiocarcinomas are highly desmoplastic, with a prominent fibrous stromal component separating small islands of malignant epithelium, histologic and cytologic confirmation of their malignancy can be challenging. Advanced cytologic tests for chromosomal polysomy such as fluorescence in situ hybridization have been shown to improve substantially the sensitivity of brush cytology for diagnosing malignancy in biliary strictures. Cytology samples with cells that show polysomy of 2 or more relevant chromosomal loci—typically chromosomes 3, 7, or 17 in the current iteration of the Vysis UroVysion (Abbott Laboratories) fluorescence in situ hybridization probe set—are highly specific for cancer (Figure 24.9).

Endoscopic Ultrasonography. Endoscopic ultrasonography with an ultrasound probe at the tip of a duodenoscope allows high-resolution evaluation of the left lobe of the liver and fine-needle aspiration of lymph nodes at the hepatic hilum. This technique is extremely useful for assessing the presence and malignancy of regional lymph nodules during staging of cholangiocarcinomas.

Management

Surgery. Hilar cholangiocarcinoma accounts for two-thirds of all cases of extrahepatic cholangiocarcinoma. Intrahepatic cholangiocarcinoma is treated with surgical resection when feasible. Tumors in the mid bile duct can be treated with resection and anastomosis of the bile duct. Distal extrahepatic cholangiocarcinomas are treated with pancreaticoduodenectomy. For hilar cholangiocarcinomas, surgical planning is more complex and preoperative evaluation of the local and regional extent of the tumor is critical. Cross-sectional imaging and cholangiography (either direct or MRCP) are necessary for appropriate patient selection and surgical planning. Current criteria that preclude resection include 1) bilateral ductal extension to secondary radicles; 2) encasement or occlusion of the main portal vein; 3) lobar atrophy with involvement of the contralateral portal vein, hepatic artery, or secondary biliary radicles; 4) peripancreatic (head only), periduodenal, posterior pancreatoduodenal, periportal, celiac, or superior mesenteric regional lymph node metastases; and 5) distant metastases. The perioperative mortality rate of hepatic resection for hilar cholangiocarcinoma is between 5% and 10% in major centers. The operation of choice for hilar cholangiocarcinoma is cholecystectomy, lobar or extended lobar hepatic and bile duct resection, regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy. With surgical resection, the 5-year survival rate is 20% to 25%.

Liver Transplant. A protocol of neoadjuvant chemoradiotherapy followed by liver transplant for patients with hilar cholangiocarcinoma or cholangiocarcinoma arising in association with primary sclerosing cholangitis has been developed at Mayo Clinic in Rochester, Minnesota. The protocol is limited to patients who have a mass with a radial diameter up to 3 cm and excludes patients who have intrahepatic peripheral cholangiocarcinoma,

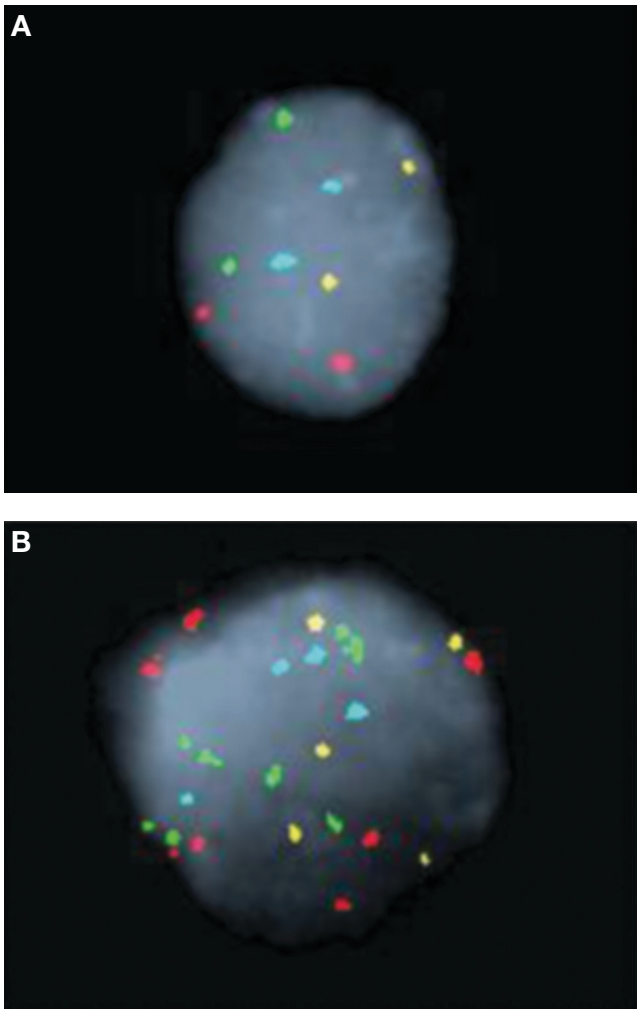

Figure 24.9. Fluorescence In Situ Hybridization for Diagnosis of Malignancy in Biliary Strictures. Fluorescent DNA probes for the centromeres of chromosomes 3 (red), 7 (green), 17 (blue), and the p16 locus at chromosome 9p21 (yellow) are hybridized to brush cytology specimens obtained from biliary strictures at endoscopic retrograde cholangiopancreatography. A, The normal diploid cell has 2 copies of each of the probes. B, The malignant polysomic cell has multiple copies of chromosomes 3, 7, 9, and 17.

metastases, or gallbladder involvement. Endoscopic ultrasonography is performed with directed aspiration to rule out involvement of regional hepatic lymph nodes. Patients are treated initially with preoperative radiotherapy (40.5-45 Gy, given as 1.5 Gy twice daily) and 5-fluorouracil. This is followed by 20- to 30-Gy transcatheter irradiation with iridium. Capecitabine is then administered until transplant. Before transplant, patients undergo a staging abdominal exploration. Regional lymph node metastases, peritoneal metastases, or locally extensive disease preclude transplant. At the time of the last published review of patients treated since 1993, overall 5-year survival on an intent-to-treat basis was 53%. Recurrence-free survival after completed liver transplant for cholangiocarcinoma was 65% at 3 years and 60% at 10 years. Similar results were achieved in a review of the aggregate results from 12 centers, with a 65% rate of recurrence-free survival after 5 years. These results exceeded those achieved with surgical resection even though all the transplant protocol patients have unresectable cholangiocarcinoma or cholangiocarcinoma arising in association with primary sclerosing cholangitis. These results also are comparable with those achieved for patients with chronic liver disease who receive a liver transplant for other indications.

Systemic Chemotherapy

Various chemotherapy agents have been evaluated for the treatment of cholangiocarcinoma, but generally there is only a limited response to these agents. The current standard of care is gemcitabine given in combination with either cisplatin or oxaliplatin. In a phase 3 clinical trial, the regimen of gemcitabine in combination with cisplatin produced tumor control (complete or partial response or stable disease) in 81.4% of patients, with a median survival of 11.7 months compared to 8.1 months for treatment with gemcitabine alone.

Maintenance of Biliary Patency. For patients with unresectable tumor causing biliary obstruction, the maintenance of biliary patency is required for substantial survival. This usually is achieved with the use of plastic endobiliary stents, which generally remain patent for 8 to 12 weeks, or metal stents, which may remain patent for more than a year. Unilateral drainage is generally sufficient for palliation of biliary obstruction and is associated with fewer complications than bilateral stenting. Photodynamic therapy, administered by intravenous infusion of the photosensitizer porfimer sodium that preferentially accumulates in the proliferating tumor tissue, followed 48 hours later with endoscopic or percutaneous application of a laser light tuned to the appropriate through a glass fiber inserted to the site of the malignant biliary stricture. Overall, photodynamic therapy appears to be associated with increased survival, improved biliary drainage, and enhanced quality of life. However, the quality of evidence is low and additional randomized trials are warranted.

Liver Metastases

Liver metastases from other primary cancer sites are the most frequent malignant liver masses. Metastases are most commonly from colorectal adenocarcinomas but also frequently occur in patients with pancreatic, esophageal, gastric, neuroendocrine, or breast cancer. Other potential primary tumors include lung cancers, lymphomas, melanomas, thyroid cancers, and renal cell carcinomas. Most often, liver metastases are multiple and distributed throughout both lobes of the liver. They tend not to have a large dominant lesion with multiple smaller satellite lesions, a feature that is more characteristic of primary liver tumors such as hepatocellular carcinoma and cholangiocarcinoma. Liver metastases have various imaging characteristics, depending on the degree of vascularity. Most commonly, they show persistent enhancement in the portal venous and venous phases of multiphasic cross-sectional CT or MRI studies. Some metastases also have a characteristic "halo" of nonenhancing tissue around the nodule. Limited disease with only a few metastatic nodules can be treated with surgical resection, stereotactic body radiotherapy, or conformal radiotherapy. For metastases that are more diffuse within the liver, locoregional therapy with TARE can be administered in combination with systemic chemotherapy appropriate for the primary tumor.

Summary

A wide range of liver mass lesions initially may or may not produce symptoms. Many masses are found incidentally during imaging for nonspecific abdominal symptoms. Accurate differentiation of

benign lesions from malignant lesions depends on obtaining a complete history, physical examination, and appropriate laboratory tests. Most benign lesions require no intervention, but an important subset requires multidisciplinary evaluation, followed by surgical resection or other treatments.

Suggested Reading

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Alcoholic Liver Disease[a]

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Epidemiology and Clinical Spectrum

Public Health Significance

Alcoholic liver disease is a major cause of morbidity and mortality worldwide. Globally, approximately 2 billion people consume alcohol, and alcohol use disorders are diagnosed in more than 75 million people—and these numbers are likely to underestimate the true burden of alcoholism. In the United States, chronic liver disease is the 12th leading cause of death, and alcohol is implicated in approximately 50% of these deaths. Also, alcoholic liver disease is a major source of health care expenditures, accounting for nearly $3 billion annually.

Clinical Spectrum

The clinical spectrum of alcoholic liver disease includes 1) simple macrovesicular steatosis (fatty liver), with or without abnormal results on liver tests; 2) severe acute steatohepatitis (alcoholic hepatitis); and 3) end-stage chronic liver disease (alcoholic cirrhosis). Fatty liver can develop in response to short, transient periods (ie, days) of alcohol abuse. It is generally asymptomatic or associated with nonspecific symptoms and is usually reversible with abstinence. This type of simple steatosis develops in 90% to 100% of regular users of alcohol. More advanced liver injury usually requires prolonged alcohol abuse over a period of years. Of note, more advanced lesions of alcoholic liver disease do not develop in the majority of people who abuse alcohol for extended periods. However, alcoholic steatohepatitis develops in 20% of these individuals, and in approximately half of those the disease progresses further to alcoholic cirrhosis. Overall, accounting for some improvement during periods of abstinence, end-stage alcoholic liver disease develops in about 20% of individuals with alcoholism.

Risk Factors

Alcohol Ingestion

The most obvious and important factors in the development of alcohol-related liver disease are dose and duration of alcohol misuse. Although alcoholic fatty liver may develop in response to short periods of alcohol abuse, even only a few days, more advanced and morbid liver injury requires prolonged alcohol abuse. In most cases, the level of ethanol consumption required for the development of advanced forms of alcoholic liver disease is 60 to 80 g of alcohol daily for men, or the approximate equivalent of 6 to 8 drinks daily for several years. In women, half this amount may cause clinically significant alcoholic liver disease. The quantity of alcohol necessary for liver injury probably does not depend on the type of alcohol consumed. However, there is considerable individual variability in the threshold of alcohol necessary for advanced alcoholic liver disease to develop. Clearly, factors other than sex and absolute ethanol consumption are important in determining which persons develop alcoholic liver disease, including ethnicity (eg, American Indians, Alaska natives), metabolic comorbidities (eg, obesity, iron overload, diabetes mellitus), coexisting liver disease (eg, viral hepatitis), and

[a] Portions previously published in Menon KV, Gores GJ, Shah VH. Pathogenesis, diagnosis, and treatment of alcoholic liver disease. Mayo Clin Proc. 2001 Oct;76(10):1021-9. Used with permission of Mayo Foundation for Medical Education and Research.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP2E1, cytochrome P450 2E1 isozyme; GGT, γ-glutamyltransferase; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; MEOS, microsomal ethanol-oxidizing system; TNF, tumor necrosis factor

genetic factors (eg, *PNPLA3* polymorphisms, alpha$_1$-antitrypsin heterozygosity).

Sex

Alcoholic liver disease is observed more commonly in men than in women, since men are statistically more likely to abuse alcohol. However, women are predisposed to the development of this disease, and more severe disease develops in women with less alcohol consumption than in men. The reason for this greater risk in women is not clear, but a similar level of alcohol consumption results in higher blood alcohol levels in women than in men. Theories to explain this include a relative deficiency of gastric alcohol dehydrogenase in women, sex differences in alcohol bioavailability, and female hormone–related effects.

Genetic and Hereditary Factors

The interindividual variability in the correlation between alcohol consumption and development of liver disease emphasizes the role of genetic factors that may predispose a person to alcohol-induced liver toxicity. Specific genetic polymorphisms have been detected in patients who have alcoholic liver disease, notably mutations in the tumor necrosis factor (TNF) promoter, the alcohol-metabolizing enzyme systems, and the *PNPLA3* gene. It also appears that milder phenotypes of diseases known to cause chronic liver disease may predispose individuals to alcohol-induced liver damage. Examples of this effect include compound heterozygosity at the hereditary hemochromatosis locus or an MZ alpha$_1$-antitrypsin phenotype. In addition to the genetic factors predisposing certain alcoholic persons to liver disease, there also is strong evidence that genetic factors predispose persons to alcoholism itself. Currently, however, no single genetic polymorphism has been shown definitively to contribute to alcoholic liver disease.

- The global burden of alcohol-related liver disease is high, accounting for significant morbidity, mortality, and cost, and its prevalence is probably underestimated.
- Alcoholic liver disease encompasses a clinicohistologic spectrum (fatty liver, alcoholic hepatitis, and cirrhosis).
- Although fatty liver occurs nearly uniformly with excess alcohol consumption, more advanced liver injury occurs in only 15% to 20% of persons who continue to abuse alcohol.
- While there is considerable variability among persons, the dose of alcohol necessary for advanced liver injury to develop is probably 60 to 80 g (6-8 drinks) daily for several years, with a significantly lower threshold for women.
- Genetic factors contribute to alcoholic liver disease by predisposing a person to alcoholism as well as to alcohol-induced liver injury.

Ethanol Metabolism and Pathophysiology

More than 1 enzyme system is capable of metabolizing alcohol in the liver. Enzymes that have received the greatest attention include alcohol dehydrogenase, aldehyde dehydrogenase, and the microsomal ethanol-oxidizing system (MEOS) (Figure 25.1). Although the peroxisomal catalase enzyme also is capable of ethanol metabolism, its physiologic role in alcohol metabolism appears to be minor.

When physiologic circumstances are normal and blood levels of alcohol are low, the enzyme of major importance is alcohol dehydrogenase. This enzyme catalyzes the conversion of alcohol to acetaldehyde, and aldehyde dehydrogenase subsequently catalyzes the conversion of acetaldehyde to acetate. Alcohol dehydrogenase catalysis changes the oxidation-reduction state in the cell by increasing the ratio of reduced nicotinamide adenine dinucleotide to the oxidized form, which has important implications for other cellular processes, including the generation of free radicals, inhibition of other enzyme systems, and accumulation of fat. Also, an isoform of alcohol dehydrogenase occurs within the gastric mucosa. Although the clinical importance of the gastric component of alcohol metabolism is debated, up to a quarter of alcohol metabolism may occur there, and sex-based differences in the activity of this isoform may help to explain why women have a lower threshold for alcohol-induced liver damage.

The MEOS is localized in the endoplasmic reticulum of the hepatocyte, whereas the alcohol dehydrogenase system operates in the cytosol. The MEOS appears to be more important in alcohol metabolism when blood levels of alcohol are moderate to high. Under normal conditions when alcohol levels are low, the role of the MEOS is much smaller than that of the alcohol dehydrogenase system. As explained by its enzyme kinetics, the MEOS has a greater role in cases of chronic alcohol use because it is induced by alcohol, thereby allowing progressively increased ethanol metabolism in alcoholics. The MEOS also converts alcohol to acetaldehyde, requiring aldehyde dehydrogenase for further metabolism. Importantly, the specific MEOS enzyme cytochrome P450 2E1 isozyme (CYP2E1) is responsible for the metabolism of various other compounds. The induction of CYP2E1 by alcohol affects blood levels of these compounds and accounts for the increased tolerance of alcoholics to sedatives. Other compounds that are metabolized rapidly in alcoholics by this process include isoniazid and acetaminophen.

Nearly half the people of eastern and southeastern Asia are deficient in aldehyde dehydrogenase activity because of the inheritance of a mutant allele. This can result in excess accumulation of aldehyde, accounting for alcohol-induced flushing symptoms in these persons. A similar flushing syndrome is observed in response to alcohol consumption when a person ingests disulfiram, which is the basis for its use in the treatment of alcoholism.

Figure 25.1. Alcohol Metabolism. Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase and cytochrome P450 2E1 isozyme (CYP2E1). In most persons, the alcohol dehydrogenase pathway is dominant; however, in alcoholic persons and those with high blood levels of alcohol, CYP2E1 is induced and has a major role in metabolism. Acetaldehyde derived from both these pathways is metabolized by aldehyde dehydrogenase to acetate. MEOS indicates microsomal ethanol-oxidizing system.

Experimental evidence suggests that the alcohol metabolite acetaldehyde may be a toxic mediator of alcohol-induced liver injury. The mechanism by which alcohol and acetaldehyde cause liver injury is being investigated. The initiation of fat accumulation within the liver appears to occur in response to the decreased oxidation and increased accumulation of fatty acids. These events may be linked to changes in the liver oxidation-reduction state induced by ethanol metabolism. Other important physiologic events that mediate liver injury include increased oxidative stress, hepatocyte apoptosis and necrosis, and deposition of collagen, with ensuing fibrosis through activation of liver stellate cells. Various cytokines, transcription factors, and intracellular signaling pathways have been implicated in these events.

- Alcohol dehydrogenase is the primary alcohol-metabolizing pathway, particularly when blood alcohol levels are low.
- The MEOS is important in alcoholics, especially when blood levels of alcohol are high. Induction of this system affects the metabolism of various xenobiotics, including sedatives and acetaminophen.
- Diminished activity of aldehyde dehydrogenase accounts for the flushing syndrome detected in a large proportion of Asians who consume alcohol and in patients who take disulfiram.

Fatty Liver

Clinical Presentation

A 22-year-old male college student has a series of laboratory tests performed during a routine checkup at the student health clinic. He is asymptomatic, and the physical examination findings are normal. He takes no medications and has no family history of liver disease. He is not sexually active and says he does not use intravenous or intranasal drugs, has not traveled recently, and has not had blood transfusions. Laboratory findings include the following: aspartate aminotransferase (AST) 65 U/L (reference range, 8-48 U/L); alanine aminotransferase (ALT) 43 U/L (reference range, 7-55 U/L); γ-glutamyltransferase (GGT) 336 U/L (reference range, 9-31 U/L); mean corpuscular volume, normal; and total bilirubin and alkaline phosphatase levels, normal. On further questioning, the patient admits to having had 6 to 10 drinks daily over the past week during student orientation.

This patient has clinical features suggestive of alcoholic fatty liver. The diagnosis and treatment are discussed below.

History and Physical Examination

Bland macrovesicular hepatic steatosis, without necroinflammatory activity, may develop in response to only a transient alcohol insult, over a period of days. The most salient historic feature is an alcohol binge. Liver steatosis results almost universally in those who consume alcohol regularly. Patients with fatty liver may be entirely asymptomatic or may complain of mild, nonspecific symptoms, including fatigue, malaise, abdominal discomfort, and anorexia. On physical examination, tender hepatomegaly may be prominent. Stigmata of chronic liver disease are absent, and in many patients, the physical examination findings are normal.

Laboratory and Radiographic Features

Laboratory studies may show mild to moderate increases in the serum levels of aminotransferases, predominantly an increase in AST. The classic 2:1 ratio of AST to ALT is not pathognomonic, but since AST exists both in the cytosol and in the mitochondria and since alcohol is a mitochondrial toxin, the AST level is typically higher than the ALT level. Minor increases in alkaline phosphatase or bilirubin (or both) may also be observed. Prothrombin time is generally normal. As in the above case, laboratory abnormalities often are noted incidentally in an asymptomatic person.

Histologic Features

Generally, liver biopsy is not necessary to establish the diagnosis of alcoholic fatty liver because the condition is benign and reversible. However, biopsy may be performed to determine whether the patient has more advanced alcoholic liver disease or another condition. The principal feature of alcoholic fatty liver in biopsy specimens is macrovesicular steatosis within hepatocytes (Figure 25.2). There are no inflammatory cells or collagen deposition. Because biopsy specimens from patients with other causes of chronic liver disease can also feature steatosis, an evaluation for these entities is sometimes advocated. An evaluation of ceruloplasmin (to screen for Wilson disease), hepatitis C status, alpha$_1$-antitrypsin phenotype, and iron stores is reasonable for young patients who have steatosis and abnormal levels of enzymes.

Prognosis and Treatment

No specific treatment other than abstinence is required for management of alcoholic fatty liver. If abstinence is achieved, alcoholic fatty liver is usually reversible. However, 20% to 30% of patients who continue to abuse alcohol chronically develop more advanced forms of alcoholic liver disease, including alcoholic hepatitis or cirrhosis (or both).

- Alcoholic fatty liver may develop in response to short periods of alcohol abuse, although it is more common with chronic alcohol abuse.
- Treatment is focused on abstinence or more judicious consumption of alcohol.

Alcoholic Hepatitis

Clinical Presentation

A 36-year-old man complains of fatigue, dark urine, and abdominal swelling. He admits to drinking a few beers daily since his teen years, but he has never had a major medical problem. Recently, he has been drinking more heavily while unemployed. He states that he has not had blood transfusions and does not use intravenous drugs. Physical examination findings are remarkable for tachycardia and low-grade fever. Prominent scleral icterus is noted, and the abdominal examination shows shifting dullness. The liver span is increased on percussion.

This patient has the clinical features typical of alcoholic hepatitis. The diagnosis and treatment are discussed below.

History and Physical Examination

A constellation of clinical symptoms, often nonspecific, are frequently observed in patients with more advanced lesions, such as alcoholic hepatitis. Men who drink more than 60 to 80 g of alcohol daily for a period of years are at risk for the development of alcoholic hepatitis; the threshold is approximately half this amount for women. Also, alcoholic hepatitis may develop in the presence or absence of underlying liver cirrhosis. The clinical presentation of patients with alcoholic hepatitis includes constitutional symptoms such as weakness, anorexia, and weight loss and other nonspecific symptoms such as nausea and vomiting.

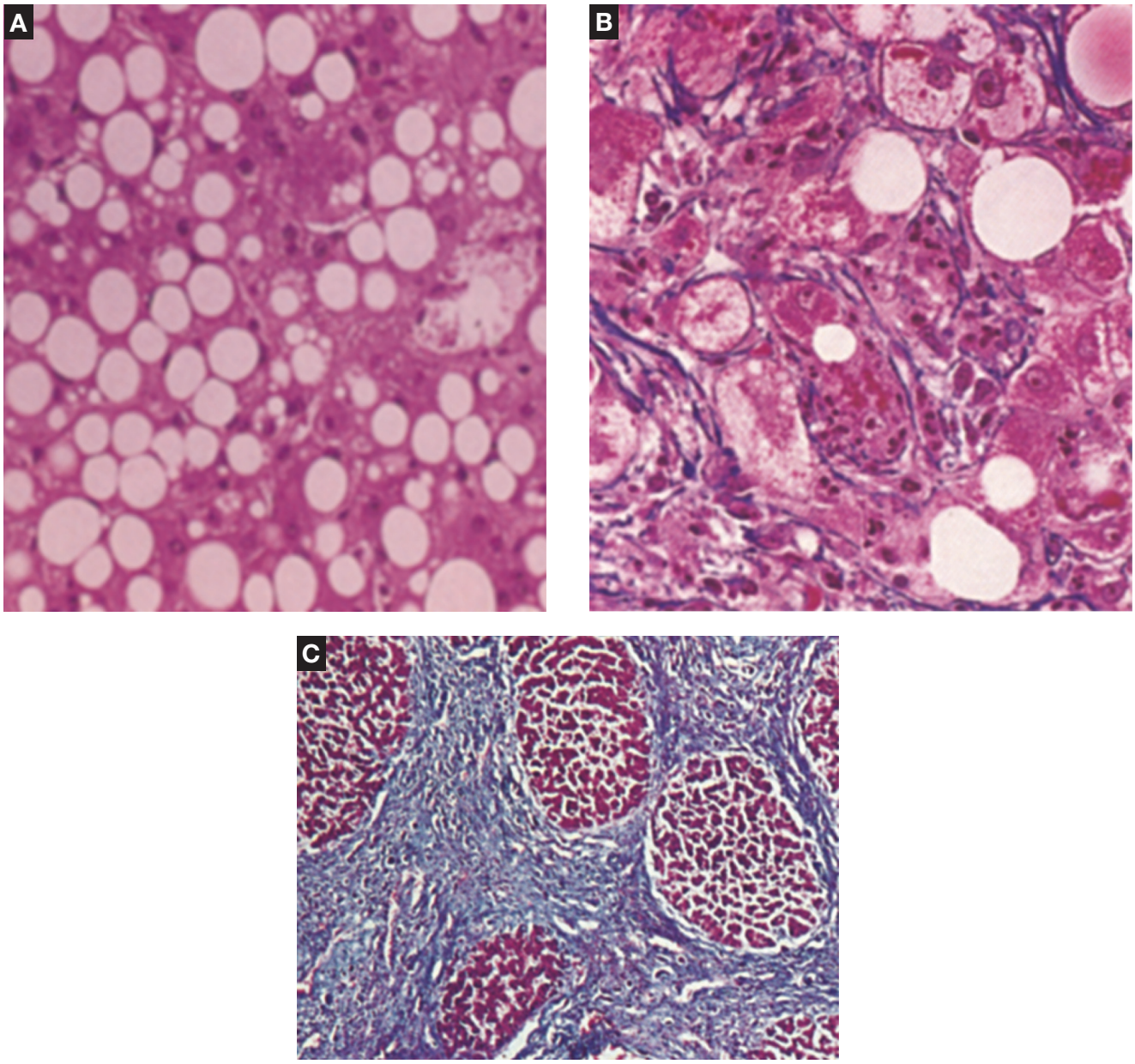

Figure 25.2. Histopathologic Features of Alcoholic Liver Disease. A, Fatty liver. Note the macrovesicular steatosis and lack of inflammation and collagen deposition (hematoxylin-eosin). B, Alcoholic hepatitis. Note the polymorphonuclear infiltrates, hepatocyte necrosis, steatosis, Mallory bodies, and variable amounts of fibrosis (hematoxylin-eosin). C, Alcoholic cirrhosis. Note the characteristic micronodular cirrhosis, although a mixed nodularity pattern is often observed (trichrome). Frequently, there is prominent secondary hemosiderosis. (Adapted from Kanel GC, Korula J. Liver biopsy evaluation: histologic diagnosis and clinical correlations. Philadelphia [PA]: WB Saunders Company; c2000. p. 39, 89, 94. Used with permission.)

Patients with severe alcoholic hepatitis may have more advanced symptoms related to portal hypertension, including gastrointestinal bleeding, ascites, and hepatic encephalopathy. It is important to identify risk factors for concomitant or alternative forms of acute and chronic hepatitis, such as viral hepatitis, Wilson disease, and drug-induced hepatitis.

The diagnosis of alcoholic hepatitis is contingent on determining whether the patient is abusing alcohol. This is not always easy because alcoholic patients and their family members often minimize or hide their alcohol use. An independent history from multiple family members is often necessary to corroborate the patient's alcohol history, and different caregivers may obtain a different history from the same interviewee. It is also critical to obtain this history early in the patient's disease course since the information is critical to subsequent decisions, such as those related to transplant candidacy, and since encephalopathy may develop later and limit the ability to obtain these historic details.

Questionnaires have been used to clarify alcohol use and abuse syndromes; however, because of their length, many of them are limited to research purposes. The most useful screening questionnaire in clinical practice is the CAGE questionnaire, which includes the following inquiries: Has the patient felt the need to *cut down* on alcohol use? Has the patient become *annoyed* with other persons' concerns about the patient's alcohol use? Does the patient feel *guilty* about the patient's alcohol use? Does the patient use alcohol in the morning as an *eye-opener*? Although

2 positive responses have a high sensitivity and positive predictive value for alcohol dependency, any positive response to these inquiries requires a more detailed investigation and should heighten the suspicion for alcohol abuse.

In patients with alcoholic hepatitis, physical examination findings are most notable for tender hepatomegaly, fever, and tachycardia. Other findings depend on the severity of liver insult, the presence or absence of concomitant cirrhosis, and the presence or absence of portal hypertension. These findings may include jaundice, splenomegaly, collateral vessels, hypogonadism, palmar erythema, asterixis, and ascites in patients with severe alcoholic hepatitis and portal hypertension. Concern for concomitant infection is common because of overlapping features of alcoholic hepatitis and infections (eg, fever, tachycardia, abdominal pain, and leukocytosis).

Laboratory and Radiographic Features

Laboratory abnormalities reflect the extrahepatic adverse effects of alcohol as well as alcohol-induced liver injury (Box 25.1). Mean corpuscular volume usually is increased, reflecting the adverse effect of alcohol on erythrocytes. The levels of triglycerides and uric acid also are frequently increased. Patients are prone to ketoacidosis. Peripheral polymorphonuclear leukocytosis is prominent, and in some cases, a dramatic leukemoid reaction may be observed. Aminotransferase levels are usually increased less than 5 to 10 times normal, but they may be higher with concomitant acetaminophen toxicity. Also, the level of AST is almost always higher than that of ALT, which is opposite of the pattern seen in nonalcoholic steatohepatitis. This in combination with other variables determines the alcoholic liver disease/nonalcoholic fatty liver disease index (http://www.mayoclinic.org/gi-rst/mayo model10.html). The index is a tool that helps distinguish nonalcoholic fatty liver disease from alcoholic hepatitis.

Abnormal results of some laboratory tests, including prothrombin time and bilirubin concentration, reflect the severity of alcohol-induced liver injury and are prognostically useful (in contrast to aminotransferase levels). Attempts have been made to use bilirubin concentration, prothrombin time, and other laboratory variables to assess the prognosis of patients who have alcoholic hepatitis. Of those assessments, the most widely used is the Maddrey discriminant function (Box 25.2). A Maddrey discriminant function greater than 32 effectively identifies patients whose short-term risk of death is higher than 50% and for whom consideration of treatment with corticosteroids is justified.

Among patients with alcoholic hepatitis, a Model for End-stage Liver Disease (MELD) score of 21 or more appears to predict short-term risk of death as well as or better than the Maddrey discriminant function threshold of 32. The MELD score and corresponding 90-day survival can be calculated on the basis of the patient's international normalized ratio (INR) and bilirubin, creatinine, and sodium values at the following website: http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-na-model.

The Lille score is another clinical prediction tool, driven largely by the change in bilirubin levels after 1 week of medical therapy, that can help in the decision to discontinue corticosteroid therapy for patients who are not having a response. Other frequently observed laboratory abnormalities that may cause diagnostic confusion or suggest multifactorial liver disease include increases in iron saturation indices and ferritin, hepatitis C virus (HCV) antibody positivity, and increased levels of autoimmune markers, such as antinuclear antibody and anti–smooth muscle antibody. Rather than reflecting the concomitant presence of hereditary hemochromatosis or autoimmune hepatitis, increases in iron indices and autoimmune markers more commonly reflect the pathogenic role of iron deposition and autoimmunity in the development of alcoholic hepatitis. In cases in which the alcohol history is questionable, a Doppler ultrasonographic study is useful to exclude alternative diagnoses, such as cholecystitis, biliary obstruction, and hepatic vein thrombosis, which may manifest in a manner similar to alcoholic hepatitis. The false diagnosis of gallstone disease can be catastrophic because of the high surgical morbidity and mortality of patients with alcoholic hepatitis.

With the inherent difficulties in obtaining a reliable history of alcohol use, several biochemical markers have been evaluated for the detection of surreptitious alcohol abuse. Many traditional serologic tests of alcohol abuse assess it indirectly by examining markers of liver injury such as AST, ALT, the AST:ALT ratio, and GGT. However, because these tests assess alcohol abuse indirectly by detecting liver injury, their sensitivity and specificity generally are less than 70%. Mean corpuscular volume also indirectly assesses alcohol abuse by evaluating the bone marrow toxicity of alcohol. Carbohydrate-deficient transferrin reflects the desialylation of transferrin that occurs

Box 25.1. Abnormal Results of Laboratory Tests in Alcoholic Hepatitis

Hematology

- Macrocytic anemia (increased MCV)
- Leukocytosis
- Thrombocytopenia

General chemistry

- Hyperglycemia
- Hyperuricemia
- Hypertriglyceridemia
- Ketosis

Liver function and injury

- Hypoalbuminemia
- Hyperbilirubinemia
- Increased prothrombin time
- Increased AST:ALT ratio (ratio, 1.5 to 2.5; total increase <10-fold)
- Increased γ-glutamyltransferase
- Increased alkaline phosphatase (mild increase)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MCV, mean corpuscular volume.

Box 25.2. Maddrey Discriminant Function

Maddrey Discriminant Function = 4.6 × (Prothrombin Time – Control Prothrombin Time) + Serum Bilirubin Concentration (mg/dL)

in response to high alcohol use, and mitochondrial AST is a specific isoform of the enzyme that is released from hepatocytes injured by alcohol. However, these tests have not been shown universally to be more effective than the less expensive AST:ALT ratio, GGT, and mean corpuscular volume.

Histologic Features

With recent advances in noninvasive liver diagnostic capabilities, the diagnosis of alcoholic hepatitis is often made without liver biopsy. However, liver biopsy is indicated if the diagnosis is in question after noninvasive evaluation. In particular, histologic examination may be useful in distinguishing coexisting or alternative liver disorders, such as hereditary hemochromatosis in persons with high iron saturation, Wilson disease in younger persons with low to low-normal ceruloplasmin levels, autoimmune hepatitis in persons with high titers of autoimmune markers, and hepatitis C in persons positive for HCV antibody. Liver biopsy, if pursued, often requires a transjugular route rather than a percutaneous route, depending on the degree of coagulopathy and thrombocytopenia.

In alcoholic hepatitis, liver biopsy specimens show several characteristic features, including centrilobular and sometimes periportal polymorphonuclear infiltrates, centrilobular hepatocyte swelling, ballooning degeneration, macrovesicular steatosis, and Mallory bodies (Figure 25.2). Often, pericentral and perisinusoidal fibrosis is detected with a trichrome stain. The terminal hepatic venules frequently are obliterated, and indeed the zone 3 region of the liver acinus shows the most prominent injury. Mallory bodies (eosinophilic-staining condensed cytoskeletal structures) are not specific for alcoholic hepatitis. However, their presence in association with other salient biopsy features strongly suggests alcoholic hepatitis. Prominent neutrophilic infiltration of hepatocytes containing Mallory bodies is termed *satellitosis*. Giant mitochondria (*megamitochondria*) are another characteristic feature. In up to 50% of cases, concomitant cirrhosis may be observed. Importantly, nonalcoholic steatohepatitis cannot be differentiated reliably from alcoholic hepatitis with liver biopsy specimens because of the overlap of histologic features.

Prognosis and Treatment

Abstinence

Abstinence is the most important factor in both short- and long-term survival of patients with alcoholic hepatitis. For patients who recover and remain abstinent, the disease may continue to improve (ie, clinical sequelae and laboratory variables improve) for as long as 6 months. Although the condition of some patients continues to deteriorate even with abstinence, the 5-year survival rate for this group is more than 60%. However, for patients who continue to drink, the 5-year survival rate is less than 30%. While medications to reduce alcohol cravings, such as acamprosate or baclofen, are attractive options, their use has not been studied well, and they should be considered only in conjunction with an experienced addiction specialist.

Nutrition

Malnutrition is almost universal among patients with alcoholic hepatitis because of concomitant poor dietary habits, anorexia, and encephalopathy. Although malnutrition was once thought to cause alcoholic liver disease, it is no longer considered to have a major role in the pathogenesis of the disease. However, maintenance of a positive nitrogen balance and provision of adequate energy requirements through nutritional support are a vital supportive treatment approach. Patients with alcoholic hepatitis generally have greater protein and energy needs because of the stress of illness and underlying malnutrition. Recommendations include caloric supplementation at 30 to 40 kcal/kg ideal body weight and protein supplementation at 1 to 1.5 g/kg ideal body weight. Provision of nutrients in excess of calculated requirements is unlikely to be of benefit. Every attempt should be made to provide adequate calories enterally. However, parenteral support may be necessary for some patients. Encephalopathy does not require protein restriction in most patients. For patients with severe encephalopathy that is exacerbated by dietary protein, branched-chain amino acid supplements can be considered. Increased use of dietary vegetable protein may be better tolerated than animal protein. Amino acid supplementation probably does not improve survival sufficiently for the added cost.

Corticosteroids

Corticosteroids have been studied extensively for the treatment of alcoholic hepatitis. Although many of the initial controlled trials did not show a benefit, further analysis suggested that patients with encephalopathy and more severe disease may benefit. Therefore, follow-up studies focused on the role of corticosteroids in the treatment of patients who had a Maddrey discriminant function greater than 32 or hepatic encephalopathy (or both) but not renal failure, infection, gastrointestinal tract bleeding, or, in some studies, severe diabetes mellitus. Some studies and meta-analyses that used these criteria showed that corticosteroid therapy provided a survival benefit for patients with a Maddrey discriminant function greater than 32 or hepatic encephalopathy (or both). A MELD score of 21 or more appears to be an acceptable alternative threshold. Currently, the use of corticosteroid therapy for alcoholic hepatitis varies among experienced hepatologists.

Pentoxifylline

Kupffer cell–derived TNF-α may have an important role in the pathogenesis of alcoholic hepatitis. The results of 1 randomized controlled study have suggested that the phosphodiesterase inhibitor, pentoxifylline, which inhibits TNF-α transcription, is of clinical benefit. Some suggest that the beneficial effects of pentoxifylline may relate to renal protection as opposed to direct liver effects. Nonetheless, because the toxicity profile of pentoxifylline is low, its use for alcoholic hepatitis is prevalent; however, confirmatory studies are needed. Other anti-TNF therapies, such as infliximab and etanercept, have been studied with mixed results and should not be used except in research protocols.

Other Pharmacotherapies Being Studied

Alcohol induces oxidative stress in the liver, resulting in an imbalance between oxidants and antioxidants. Looking for a way to decrease oxygen consumption by the liver, investigators have studied the role of propylthiouracil in treating alcoholic hepatitis, but the results have been inconclusive. Colchicine has also been evaluated for treating alcoholic hepatitis, but no clinical benefit has been found. Other hepatoprotective compounds, such as *S*-adenosyl-L-methionine, phosphatidylcholine, milk thistle, and *N*-acetylcysteine have been evaluated but are not widely accepted.

Management of Portal Hypertension

Complications of portal hypertension may develop in patients with alcoholic hepatitis regardless of the presence or absence of underlying cirrhosis. This clinical observation is supported by studies showing that alcohol directly increases portal pressure, and it emphasizes the importance of the vascular component of intrahepatic resistance and portal hypertension. Hepatic encephalopathy, bleeding esophageal varices, ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome are complications of portal hypertension commonly encountered in patients with alcoholic hepatitis. The management of these complications is discussed elsewhere in this book.

Treatment of Infection

Because of underlying malnutrition, liver cirrhosis, and iatrogenic complications, infection is one of the most common causes of death of patients with alcoholic hepatitis. The patients must be evaluated carefully for infections, including spontaneous bacterial peritonitis, aspiration pneumonia, and lower extremity cellulitis. These infections should be treated aggressively with antibiotics. However, fever and leukocytosis are common in patients with alcoholic hepatitis, even without infection.

Liver Transplant

A recent trial demonstrated that early liver transplant improved survival among a highly selected group of patients not responding to medical therapy. While most patients with alcoholic hepatitis are not suitable candidates for liver transplant, less than 6 months of abstinence is not itself an absolute contraindication to liver transplant. Thus, patients not responding to medical therapy may warrant discussion with a liver transplant center team, although this is a highly controversial area with significant practice variation among transplant centers.

- Alcoholic hepatitis may occur in the presence or absence of preexisting liver cirrhosis.
- Liver biopsy should be considered if the cause of hepatitis is questioned and specific treatments of other entities are contemplated.
- Histologic features cannot reliably differentiate alcoholic hepatitis from nonalcoholic steatohepatitis. The distinction is made best on the basis of the clinical history and the pattern of laboratory test results.
- For most patients, the treatment of alcoholic hepatitis includes abstinence, supportive care, and management of malnutrition, infection, and complications of portal hypertension.

Alcoholic Cirrhosis

Clinical Presentation

A 56-year-old salesman is admitted to the hospital with a 2-hour history of hematemesis and dizziness. His history is remarkable for symptoms of fatigue and lower extremity edema. His wife notes that his memory has been poor recently and that he has been a "social drinker" for many years, having a few martinis with clients and during business trips. Physical examination findings are notable for orthostasis, temporal wasting, spider angiomas on the chest, and bilateral pitting edema of the lower extremities. His skin is jaundiced, and a liver edge is palpable and firm. The tip of the spleen is palpable upon inspiration. Rectal examination shows melena in the vault. There is prominent asterixis.

This patient has the clinical features typical of alcoholic cirrhosis. The diagnosis and treatment are discussed below.

History and Physical Examination

Among persons with a clinical history of marked and prolonged alcohol abuse, liver cirrhosis eventually develops in only about 20%. The presence or absence of symptoms is due largely to the presence or absence of liver decompensation. Patients with cirrhosis and compensated liver function may have minimal symptoms. The symptoms of patients with liver decompensation reflect the severity of portal hypertension, malnutrition, and degree of synthetic liver dysfunction and include nonspecific fatigue, weakness, and anorexia. More specific symptoms are related to the presence of specific complications of cirrhosis and portal hypertension, including gastrointestinal tract bleeding, ascites, encephalopathy, renal failure, and hepatocellular carcinoma. Physical examination findings may include stigmata of chronic liver disease (spider angiomas and palmar erythema), complications of portal hypertension (ascites, splenomegaly, asterixis, and pedal edema), signs of excess estrogen (gynecomastia and hypogonadism), and signs of systemic alcohol toxicity (peripheral neuropathy, dementia, and Dupuytren contracture).

Laboratory and Radiographic Features

Prominent laboratory abnormalities include an increase in prothrombin time and bilirubin and a decrease in albumin, which are reflected in an increased Child-Turcotte-Pugh score. Imaging findings may be suggestive of cirrhosis and ensuing portal hypertension, as indicated by heterogeneous liver echotexture, splenomegaly, collateralization, and ascites on ultrasonography. Computed tomography may show changes in liver contour, splenomegaly, collateralization, or ascites. Patients with cirrhosis are at risk for hepatocellular carcinoma and should be evaluated biannually with ultrasonography with or without serum alpha-fetoprotein levels, as should patients who have had recent clinical decompensation.

Histologic Features

Traditionally, alcoholic cirrhosis is classified as a micronodular cirrhosis (Figure 25.2). However, in many cases, larger nodules also develop, leading to mixed micro-macronodular cirrhosis. The earliest collagen deposition occurs around the terminal hepatic venules, and progression to pericentral fibrosis portends irreversible architectural changes. Hemosiderin deposition is often prominent. In patients with alcoholic cirrhosis who continue to drink actively, many of the histologic features of alcoholic hepatitis also are present.

Prognosis and Treatment

A good prognosis depends on the absence of liver decompensation and complications of portal hypertension and on the patient's ability to maintain abstinence. The prognosis for patients with cirrhosis who are well compensated and able to maintain abstinence is reasonably good (5-year survival rate >80%). Even for patients with decompensation, the 5-year survival rate with abstinence is more than 50%. However, patients who continue to drink have a much worse prognosis (5-year survival rate <30%).

The only established effective treatment for alcoholic cirrhosis is liver transplant. Currently, alcoholic liver disease is the second most common indication for liver transplant (after chronic hepatitis C) in adults in the United States. However, less than 20% of patients with end-stage alcoholic liver disease undergo transplant. Despite perceptions to the contrary, survival rates after

transplant for alcoholic liver disease are comparable to those after transplant for other indications. In fact, the risk of acute cellular rejection is actually lower for persons undergoing transplant for alcoholic liver disease than for those with other conditions.

A major issue in maintaining excellent outcomes for this population focuses on identifying candidates with a low risk of recidivism after transplant. Alcohol relapse after transplant varies among centers and is difficult to quantify accurately, but it is probably about 15% to 30%. Although detecting surreptitious alcohol use after transplant is often difficult, the low incidence of graft loss from recurrent alcoholic liver disease suggests that most patients who return to drinking after transplant do not drink to the point of endangering the graft. However, heavy alcohol abuse after liver transplant can cause rapid development of cirrhosis in the graft. Alcohol use also may interfere with compliance in taking immunosuppressive medications and alter the perception of the general public toward liver transplant, thus adversely affecting potential organ donors. Therefore, selecting patients who are appropriate for liver transplant requires a multidisciplinary team involving a hepatologist, transplant surgeon, addiction specialist, psychiatrist, and social worker. Currently, many transplant centers advocate 6 months of abstinence, appropriate addiction treatment, and demonstrated family and social support before performing a liver transplant for alcohol-related cirrhosis.

- Alcohol causes micronodular or mixed micro-macronodular cirrhosis in about 20% of prolonged alcohol abusers.
- Alcoholic cirrhosis is currently the second most common indication for liver transplant, which is the only curative treatment.
- Only a small proportion of patients with alcoholic cirrhosis undergo transplant, because of various psychosocial barriers.
- Transplant outcomes for alcoholic liver disease are comparable to those for most other indications.

Special Clinical Situations

Alcohol and Hepatitis C

The prevalence of HCV infection among alcoholic persons is 10 times that among the population at large. Although this may be explained partly by increased risk factors of HCV transmission in some alcoholic patients, a proportion of these patients have no identifiable risk factors. Also, patients with HCV infection who are alcoholic or drink in excess have more aggressive disease, often at a younger age, and have a worse prognosis than patients who have HCV infection alone. Furthermore, HCV RNA levels are higher, the histologic features of the liver appear more progressive, and the response to therapy for hepatitis C is worse for patients with HCV infection who drink alcohol in excess. It is unclear whether alcohol synergistically damages the liver in patients with HCV infection or, alternatively, facilitates progression of HCV disease through increased susceptibility by host immune factors.

Patients with alcoholic liver disease who have concomitant viral hepatitis have a risk almost 5-fold greater for the development of hepatocellular carcinoma than patients without concomitant viral hepatitis. Identifying which process is causative in liver injury in patients with both conditions can be difficult; however, assessing liver biopsy findings and aminotransferase patterns can be useful because both of these are different in HCV infection and alcoholic liver injury. Because the alcohol threshold necessary to exacerbate the course of HCV infection has not been determined, patients with HCV infection should not consume alcohol.

Alcohol and Acetaminophen

Patients who regularly use alcohol are at increased risk for acetaminophen-induced hepatotoxicity. An acetaminophen dosage of as little as 2.5 to 3 g daily may result in pronounced toxicity. The reason for this is that both alcohol and acetaminophen are metabolized in part by CYP2E1, an enzyme in the MEOS. With the induction of this enzyme by alcohol, a greater proportion of acetaminophen is metabolized by this pathway than by the sulfation and glucuronidation detoxification pathways. The byproduct of acetaminophen metabolism by CYP2E1 is *N*-acetyl-*p*-benzoquinone imine, which is toxic to the liver. The accumulation of this compound in conjunction with diminished antioxidant defenses in the liver (glutathione) lowers the threshold of acetaminophen toxicity in patients using alcohol.

The clinical presentation of regular alcohol users with acetaminophen toxicity is distinct from that of patients with alcoholic hepatitis. Aminotransferase levels are markedly increased—often more than 1,000 U/L—which is distinctly unusual for alcoholic hepatitis. This situation may arise when a regular alcohol user has a minor illness, discontinues alcohol use, and takes moderate doses of acetaminophen (the so-called therapeutic misadventure). Ironically, discontinuation of alcohol actually perpetuates this problem since more cellular resources are then available for acetaminophen metabolism. Therefore, patients who use alcohol regularly should not use acetaminophen without the supervision of a physician and should limit their intake to 2 g daily. In contrast, acetaminophen is actually the analgesic of choice for patients with cirrhosis, including alcoholic cirrhosis, as long as the patient is not currently using alcohol.

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26

Vascular Diseases of the Liver[a]

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Vascular diseases of the liver can be divided into disorders of hepatic inflow (ie, disorders of portal venous inflow and disorders of hepatic arterial inflow) and disorders of hepatic venous outflow (Box 26.1). For a better understanding of the vascular diseases of the liver, a concise review of the vascular anatomy of the liver is important.

Anatomy of the Splanchnic Circulation

The splanchnic circulation comprises the arterial blood supply and venous drainage of the entire gastrointestinal tract from the distal esophagus to the midrectum and includes the spleen (which is why splenomegaly and thrombocytopenia develop in the presence of portal hypertension), pancreas, gallbladder, and liver. The arterial system is derived from the celiac artery and the superior and inferior mesenteric arteries. The superior mesenteric artery arises from the abdominal aorta just distal to the celiac trunk. The superior mesenteric artery gives off 3 sets of branches: 1) several small branches to the pancreas and duodenum before entering the mesentery, 2) 3 large arteries that supply the proximal two-thirds of the large bowel, and 3) during its course through the mesenteric root, an arcade of arterial branches to supply the jejunum and ileum. The branches given off in the mesentery form a row of arterial arcades that terminate in the arteriae rectae of the wall of the small bowel. The venous drainage has a similar pattern, with the venae rectae forming a venous arcade that drains the small bowel. These join with the ileocolic, middle colic, and right colic veins to form the superior mesenteric vein.

The arterial routes of the splanchnic circulation, except for the hepatic artery, eventually empty into the portal venous system through the splenic vein and superior and inferior mesenteric veins. The portal vein, formed by the convergence of the splenic and superior mesenteric veins, constitutes the primary blood supply to the liver. After perfusing the liver, venous blood reenters the systemic circulation through the hepatic veins and suprahepatic inferior vena cava.

Reminiscent of the lungs, the liver receives a dual blood supply. The 2 sources are portal venous blood (derived from the mesenteric venous circulation, including the digestive tract, spleen, and pancreas) and hepatic arterial blood (usually from the celiac artery). Total hepatic blood flow constitutes nearly 30% of total cardiac output. The portal venous inflow comprises 65% to 75% of hepatic blood inflow, and the hepatic artery comprises approximately 25% to 35%. However, approximately 50% of the liver's oxygen requirements is delivered by hepatic arterial blood.

The hepatic vascular bed is a low-pressure system that can maintain a large volume of blood. Sinusoidal blood collects within terminal hepatic venules and reenters the systemic circulation through the hepatic veins and inferior vena cava. The caudate lobe of the liver maintains a separate venous drainage, accounting for the compensatory hypertrophy of this lobe often observed in chronic liver disease associated with outflow obstruction of the major hepatic veins (Budd-Chiari syndrome).

Disorders of Portal Venous Inflow

Acute Mesenteric Venous Thrombosis

Acute mesenteric venous thrombosis is discussed in Chapter 12, "Vascular Disorders of the Gastrointestinal Tract."

[a] Portions previously published in Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. N Engl J Med. 2001 Dec 6;345(23):1683-8. Used with permission.

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; TIPS, transjugular intrahepatic portosystemic shunt

Box 26.1. Vascular Diseases of the Liver

Disorders of portal venous inflow

- Acute mesenteric or portal venous thrombosis
- Chronic mesenteric or portal venous thrombosis

Disorders of hepatic arterial inflow

- Hepatic artery thrombosis
- Hepatic arteriovenous fistula
- Ischemic hepatopathy

Disorders of hepatic venous outflow

- Venoocclusive disease
- Budd-Chiari syndrome

Chronic Mesenteric Venous Thrombosis

Chronic mesenteric venous thrombosis is very different from the acute form. Lack of visualization of the superior mesenteric vein on computed tomography or duplex ultrasonography in conjunction with extensive collateral venous drainage suggests the diagnosis of chronic mesenteric venous thrombosis. Angiography can help confirm the diagnosis but rarely is required. Although many patients present with nonspecific symptoms of several months' duration, an increasing proportion are being identified through imaging studies performed for unrelated reasons. These patients may be asymptomatic with respect to the primary event; hence, the time of the thrombotic event often is unclear. Patients in whom the thrombosis extends to involve the portal vein or splenic vein (or both) may experience portal hypertension and esophageal varices, with the attendant complications of variceal bleeding. They also may have splenomegaly and hypersplenism.

Chronic mesenteric venous thrombosis should be differentiated from isolated splenic vein thrombosis due to pancreatic neoplasm or chronic pancreatitis. Splenic vein thrombosis, often called *sinistral* (or left-sided) *portal hypertension*, is related to a local effect on the splenic vein and is not usually a disorder of the thrombotic pathway. Thus, anticoagulation is not warranted for sinistral portal hypertension.

Patients with isolated chronic mesenteric venous thrombosis often remain asymptomatic because of the development of extensive venous collaterals. Occasionally, some patients have gastrointestinal tract hemorrhage, and the use of a pharmacologic agent such as propranolol is recommended to prevent variceal bleeding. Endoscopic therapy is used both to control active bleeding and to prevent rebleeding. Surgical intervention (eg, portosystemic shunts) is restricted to patients whose bleeding cannot be controlled with conservative measures and who have a patent central vein for shunting. When thrombosis is extensive and no large vein is suitable for anastomosis, nonconventional shunts (eg, anastomosis of a large collateral vein with a systemic vein) may be considered. Surgical expertise for such shunts is present in a small number of referral centers. For refractory variceal bleeding, gastroesophageal devascularization may be considered. For patients with thrombophilia, anticoagulation may be initiated after the risk of bleeding has been decreased by the use of β-blockers or, if bleeding has occurred, surgical shunts.

Disorders of Hepatic Arterial Inflow

Hepatic Artery Thrombosis

Aside from patients who have had liver transplant, the prevalence of hepatic artery thrombosis is not certain. Hepatic artery thrombosis is the cause of considerable morbidity and mortality in approximately 7% of adult deceased donor transplant recipients, in up to 30% of adult living donor transplant recipients, and in perhaps as many as 40% of pediatric patients undergoing orthotopic liver transplant. The problem is more extensive in the pediatric age group because of the smaller caliber of the vessels involved and the probable greater fluctuation in the concentration of coagulation factors.

Several risk factors are related to the development of hepatic artery thrombosis in adults, with the type of transplant (living donor or deceased donor) and the technical aspects of the arterial anastomosis being the most important risk factors for early thrombosis. Other risk factors are older recipients, clotting abnormalities, tobacco use, and infections by agents such as cytomegalovirus. Late hepatic artery thrombosis has been associated with chronic rejection and blood type–incompatible grafts.

The clinical presentation of hepatic artery thrombosis can vary from a mild increase in the serum level of aminotransferases to fulminant hepatic necrosis. Early hepatic artery thrombosis has a more severe clinical course, and late hepatic artery thrombosis generally has a milder course. There is no agreement about a time that distinguishes *early* from *late* hepatic artery thrombosis. However, the later that hepatic artery thrombosis develops after liver transplant, the less severe the clinical presentation.

Early hepatic artery thrombosis results in massive injury to hepatocytes and bile duct epithelial cells. Ischemic damage to the bile ducts leads to dehiscence of the biliary anastomosis, bile duct strictures (typically nonanastamotic), and intrahepatic abscesses. Thus, biliary sepsis may be a common presentation of early hepatic artery thrombosis. However, one-third of episodes of early hepatic artery thrombosis may be asymptomatic.

Hepatic artery thrombosis can be diagnosed with duplex ultrasonography, but angiography may be necessary to confirm the diagnosis. When hepatic artery thrombosis is detected early after liver transplant, surgical correction usually is recommended. Patients who have early hepatic artery thrombosis with significant graft dysfunction should be listed for retransplant.

Hepatic Artery Aneurysm

Although aneurysm of the hepatic artery (Figure 26.1) is rare, it is the fourth most common abdominal aneurysm. The aneurysms are usually small (<2 cm in diameter) and involve the main hepatic artery. Causes of hepatic artery aneurysms include atherosclerotic vascular diseases, infections (eg, bacterial endocarditis, liver abscess, syphilis, tuberculosis), and trauma from liver biopsy. The hepatic artery commonly is involved in polyarteritis nodosa, manifested as symptoms related to thrombosis, rupture, or dissection of the aneurysm.

Most hepatic artery aneurysms are discovered incidentally. If they are symptomatic, the first and dominating symptom is severe abdominal pain, suggesting dissection. Vague abdominal pain in these patients is related to compression of surrounding structures. Rupture of a hepatic artery aneurysm causes massive intraperitoneal hemorrhage or hemobilia manifested as abdominal pain, jaundice, and gastrointestinal tract bleeding. Hemobilia is usually a manifestation of an intrahepatic aneurysm.

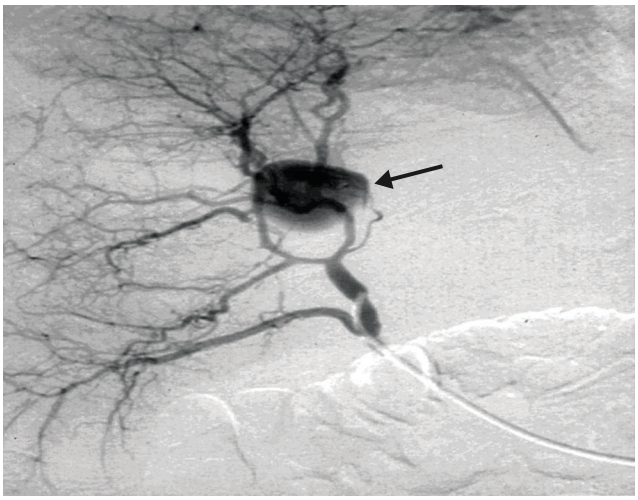

Figure 26.1. Aneurysm of the Hepatic Artery. Selective hepatic angiogram shows an aneurysm (arrow) of the intrahepatic portion of the hepatic artery.

The treatment of a ruptured aneurysm is emergency surgery or embolization of the aneurysm in patients who are not optimal candidates for surgery. For asymptomatic patients, treatment is debated. Clearly, aneurysms larger than 2 cm in diameter require treatment, and those between 1 and 2 cm in diameter may be treated. For aneurysms smaller than 1 cm in diameter, follow-up at 6-month intervals is reasonable. Treatment includes interventional radiologic approaches to embolize and occlude the aneurysm, ligation at surgery, or excision of the aneurysm and reconstruction of the artery. Intrahepatic aneurysms may also be treated with liver resection.

Hepatic Artery–Portal Vein Fistulas

Hepatic artery–portal vein fistulas are rare causes of portal hypertension. Although fistulas within the liver usually are iatrogenic (the result of liver biopsy), they may be related to neoplasms or hereditary hemorrhagic telangiectasia (HHT) (Osler-Weber-Rendu disease). A hepatic artery–portal vein fistula should be suspected in a patient who has acute onset of abdominal pain and ascites, especially if associated with gastrointestinal tract bleeding, because rupture of the artery into the portal vein causes an acute increase in portal pressure. These fistulas may be accompanied by abdominal bruits in most patients. Hepatic artery–portal vein fistulas are treated with coil embolization or surgical ligation. If untreated, a hepatic artery–hepatic vein fistula may result in high-output congestive heart failure. The best treatment is embolization and occlusion of the fistula, except in the presence of HHT, when embolization is absolutely contraindicated.

Ischemic Hepatopathy

In patients with congestive heart failure, portal blood flow is minimal; thus, the major contribution of oxygenated blood to the liver is from the hepatic artery. In congestive heart failure, episodes of hypotension, as associated with arrhythmias, diminish hepatic arterial input and result in ischemic necrosis of the liver. Typical manifestations of ischemic hepatopathy are rapid increases (ie, within 24-48 hours) in the serum levels of aminotransferases (aspartate aminotransferase and alanine aminotransferase) to several thousand units per liter (sometimes >10,000 U/L). These values rapidly return to less than 100 U/L in 5 to 7 days. No specific treatment is required other than control of the cardiac condition. Extensive ischemic hepatopathy may result in acute liver failure.

Other causes of ischemic hepatopathy are hypovolemic shock of any cause and obstructive sleep apnea. Postoperative patients especially are prone to ischemic liver damage because they often have coexisting arterial hypotension and hypoxemia. Furthermore, hepatic blood flow may be reduced by anesthetic agents. This problem may be of particular concern for patients who have open heart surgery. The typical histologic finding in these patients with ischemic liver damage is centrilobular hepatic necrosis (zone 3). The severity of liver damage is related to the duration of hypotension and the degree of hypoxemia.

Hereditary Hemorrhagic Telangiectasia

The criteria for diagnosing HHT include a history of epistaxis, a family history of HHT, mucocutaneous telangiectasia, and visceral involvement, which can be hepatic, gastrointestinal, neurologic, or pulmonary. Three of these criteria are required for the diagnosis of HHT.

The vascular malformation within the liver of patients with HHT results in fistulas 1) between the hepatic artery and the hepatic vein (the most common abnormality), 2) between the hepatic artery and the portal vein, or 3) between the portal vein and the hepatic vein (or a combination of these 3). Previously, the most common liver disease in patients with HHT was transfusion-related viral hepatitis, but currently the most common manifestation is high-output cardiac failure resulting from hepatic artery–hepatic vein fistulas. Additional abnormalities include recurrent cholangitis due to the diversion of hepatic arterial blood, to either the hepatic vein or the portal vein; portal hypertension as a result of hepatic artery–portal vein fistulas or nodular regenerative hyperplasia; and hepatic encephalopathy due to fistulas between the portal vein and the hepatic vein. Embolization of these fistulas is not recommended because of the high risk of liver abscesses. This is probably related to most patients having some degree of a portal vein–hepatic vein fistula, and once the hepatic artery is occluded, there is neither hepatic arterial blood nor portal venous blood to the involved segment of the liver. Liver transplant has been performed to treat HHT and is best indicated for patients who have recurrent cholangitis.

Disorders of Hepatic Venous Outflow

Venoocclusive Disease

Venoocclusive disease, or sinusoidal obstruction syndrome, results from occlusion of the central and sublobular hepatic veins. In the United States, the most common cause of venoocclusive disease is preconditioning therapy for bone marrow transplant. Other causes include radiation to the liver, antineoplastic drugs such as azathioprine and 6-mercaptopurine, and ingestion of alkaloids containing pyrrolizidine.

The following discussion is predominantly about venoocclusive disease of the liver in relation to patients undergoing bone marrow transplant. For these patients, the incidence of venoocclusive disease was approximately 50% when cyclophosphamide and total body radiotherapy were used as intensive conditioning therapy before transplant, and the mortality rate was 20% to 40%.

Table 26.1. Diagnostic Criteria for Venoocclusive Disease

Criteria	*Weeks After BMT*	*Weight Gain, %*	*Other Required Findings*
Baltimore	≤3	>5	Hepatomegaly Ascites
Seattle	≤3	>2	Bilirubin >2 mg/dL Hepatomegaly RUQ pain

Abbreviations: BMT, bone marrow transplant; RUQ, right upper quadrant.

Currently, the incidence of venoocclusive disease is low because cyclophosphamide and high-dose radiotherapy are no longer used. Early changes are related to hemorrhage in zone 3, as seen in liver biopsy specimens. Diagnostic criteria include subendothelial thickening of at least 1 terminal hepatic venule in association with luminal narrowing.

The pathogenesis of venoocclusive disease is not well defined. It probably results from a combination of endothelial injury and activation of clotting mechanisms. It has been hypothesized that the depletion of glutathione in zone 3 hepatocytes makes them more prone to damage by antineoplastic agents such as busulfan. The resulting accumulation of oxygen free radicals leads to zone 3 necrosis and subsequent endothelial damage.

The diagnostic criteria for venoocclusive disease are listed in Table 26.1. Bilirubin levels greater than 15 mg/dL are associated with poor outcome. Treatment of venoocclusive disease is difficult. Prophylactic strategies have included administration of heparin, prostaglandins, or ursodeoxycholic acid. Because of the lack of large randomized studies, it is difficult to determine the benefits of any of these therapies. The treatment of established venoocclusive disease also is debated. Tissue plasminogen activator and heparin have been administered to patients at high risk for dying of complications of venoocclusive disease. If there is no response to thrombolytic therapy, either a surgical shunt or a transjugular intrahepatic portosystemic shunt (TIPS) may be used. Although the initial results with portosystemic shunts may be beneficial, the long-term outcome for patients who require shunts is poor because these patients usually have severe venoocclusive disease and intervention generally delays, but does not prevent, a fatal outcome.

Budd-Chiari Syndrome

Budd-Chiari syndrome is a heterogenous group of disorders characterized by obstruction of hepatic venous outflow. The site of obstruction may be at the level of small hepatic venules, large hepatic veins, or the inferior vena cava. Obstruction at the level of the central and sublobular hepatic venules traditionally has been called *hepatic venoocclusive disease*. In countries such as Japan and India, obstruction of the inferior vena cava by membranes or webs or segmental narrowing of the vessel also may obstruct hepatic venous outflow.

Etiology

The main predisposing causes of Budd-Chiari syndrome include a hypercoagulable state, tumor invasion of the hepatic venous outflow tract, and miscellaneous causes. In some patients, no clear etiologic factor is discernible. Increasingly, the presence of multiple underlying disorders that cause Budd-Chiari syndrome is being recognized.

Hematologic abnormalities, particularly myeloproliferative disorders, are detected in up to 87.5% of patients with Budd-Chiari syndrome. Overt polycythemia vera is the most common disorder encountered. Erythropoietin levels and demonstration of *JAK* mutations have been used to diagnose occult primary myeloproliferative disorders in patients otherwise thought to have idiopathic Budd-Chiari syndrome. Both fulminant and chronic forms of the syndrome have been described for patients with paroxysmal nocturnal hemoglobinuria. Increasingly, inherited deficiencies of protein C, protein S, and antithrombin are being reported in association with the syndrome. Protein C and protein S are vitamin K–dependent proteins that are synthesized in the liver and endothelial cells and act as fibrinolytic agents. Antithrombin is a vitamin K–independent protease inhibitor that is synthesized in the liver and neutralizes activated clotting factors by forming a complex with a specific serine protease. Deficiencies of any of these proteins can result in both arterial thrombosis and venous thrombosis, but the correlation between the levels of protein C and protein S and the risk of thrombosis is not precise. In several patients with Budd-Chiari syndrome, protein C deficiency has also been associated with an underlying myeloproliferative disorder. The diagnosis is sometimes difficult because these proteins can become deficient in patients with impaired liver function. Normal levels of factors II and VII in patients with Budd-Chiari syndrome or deficiencies of protein C and protein S in family members may point toward an inherited disorder.

The factor V Leiden mutation has been reported in approximately 23% of patients with Budd-Chiari syndrome. This mutation, caused by the substitution of an arginine residue by glutamine at position 506 in the factor V molecule, abolishes a protein C cleavage site in factor V and prolongs the thrombogenic effect of factor V activation. The term *resistance to activated protein C* is another name for this condition. Although about 2.9% to 6% of people of European descent are believed to be heterozygous for this mutation, the relative risk of thrombosis is thought to be low. In addition to being a sole cause of Budd-Chiari syndrome, this mutation has been reported to occur also in combination with other prothrombotic disorders.

Clinical Manifestations

The underlying pathophysiologic abnormality in Budd-Chiari syndrome is an increase in sinusoidal pressure caused by obstruction of hepatic venous outflow. This results in hypoxic damage to the hepatocytes and increased portal venous pressure. Continued obstruction of hepatic venous outflow leads to further hepatic necrosis, ultimately resulting in cirrhosis. Because the caudate lobe drains directly into the inferior vena cava, it is not damaged. In fact, the caudate lobe hypertrophies, and this may, to various degrees, obstruct the inferior vena cava. The clinical presentation of Budd-Chiari syndrome depends on the extent and rapidity of the occlusion of the hepatic vein and whether collateral circulation has developed to decompress the liver. Vague right upper quadrant abdominal pain is the most common presenting symptom of the syndrome, and ascites is the most common abnormality noted on physical examination. Some patients with hepatic vein thrombosis are asymptomatic, presumably as a result of occlusion of only 1 or 2 hepatic veins and decompression of the portal system through the development of large intrahepatic and portosystemic collaterals.

Investigations

Doppler ultrasonography of the liver is the initial investigation of choice for patients with suspected Budd-Chiari syndrome; it provides visualization of the hepatic veins, splenic vein, portal vein, and inferior vena cava. Areas of necrosis are seen better with contrast-enhanced computed tomography and magnetic resonance imaging.

Venography or liver biopsy is not necessary after Budd-Chiari syndrome has been diagnosed with noninvasive studies. However, if the clinical suspicion of Budd-Chiari syndrome is high, especially for a patient with a fulminant or acute presentation, contrast venography may be necessary if noninvasive imaging is not diagnostic. The characteristic appearance of the hepatic veins in Budd-Chiari syndrome is that of a spiderweb, with an extensive collateral circulation. Also, the inferior vena cava may be compressed by an enlarged caudate lobe, or it may show thrombus.

In addition to establishing the diagnosis of hepatic vein thrombosis, it is important to identify an underlying cause to determine management strategies. An appropriate hematologic workup should be performed to exclude the various disorders outlined in Box 26.2, including evaluation for *JAK2* mutations to determine whether the patient has a myeloproliferative disorder.

Box 26.2. Causes of Budd-Chiari Syndrome

- **Common causes**
  - Hypercoagulable states
    - Inherited
      - Factor V Leiden mutation
      - Prothrombin mutation
    - Acquired
      - Myeloproliferative disorders
      - Cancer
      - Pregnancy
      - Oral contraceptive use
- **Uncommon causes**
  - Hypercoagulable states
    - Inherited
      - Antithrombin deficiency
      - Protein C deficiency
      - Protein S deficiency
    - Acquired
      - Paroxysmal nocturnal hemoglobinuria
      - Antiphospholipid syndrome
  - Tumor invasion
    - Hepatocellular carcinoma
    - Renal cell carcinoma
    - Adrenal carcinoma
  - Miscellaneous
    - Aspergillosis
    - Behçet syndrome
    - Inferior vena cava webs
    - Trauma
    - Inflammatory bowel disease
    - Dacarbazine therapy
  - Idiopathic

Adapted from Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. N Engl J Med. 2004 Feb 5;350(6):578-85. Used with permission.

Management

The aims of treatment of Budd-Chiari syndrome are to relieve obstruction of the hepatic outflow tract, to identify and treat the underlying cause, and to relieve symptoms. Treatment options include medical management, surgical portosystemic shunting, TIPS, and liver transplant (Table 26.2). Although most patients who have Budd-Chiari syndrome can be offered some form of definitive therapy, those in whom the syndrome is due to extensive malignant disease are offered only palliative care because of the extremely poor prognosis with this condition.

Medical management consists of diuretic therapy for the treatment of ascites, anticoagulation to prevent extension of venous thrombosis, and treatment of the underlying cause. Approximately 20% of patients can be managed with this approach. If this approach fails, intervention to enhance hepatic venous outflow is the next step. Ideal candidates for angioplasty include patients with inferior vena cava webs or focal hepatic vein stenosis; thrombolytic therapy is used infrequently but is administered best by direct infusion to the site of the clot.

The aim of portosystemic shunting is to use the portal vein to provide a venous outflow tract for the liver in order to reverse hepatic necrosis and to prevent chronic sequelae of obstruction of hepatic venous outflow. The optimal candidates for surgical shunting are patients with a subacute presentation in whom ascites is not severe, liver function is preserved, and the disease course is smoldering. Patients with acute Budd-Chiari syndrome may need a less invasive procedure, such as TIPS. Covered stents have increased the long-term patency of TIPS, making this the preferred method of performing a portosystemic shunt in most patients. Indications for liver transplant in Budd-Chiari syndrome include 1) end-stage chronic liver disease, 2) fulminant liver failure, and 3) deterioration of liver function in spite of portosystemic shunting.

Table 26.2. Management of Budd-Chiari Syndrome (BCS)

Treatment	*Indication*	*Advantages*	*Disadvantages*
Thrombolytic therapy	Acute thrombosis	Reverses hepatic necrosis No long-term sequelae	Risk of bleeding Limited success
Angioplasty with and without stenting	IVC webs IVC stenosis Focal hepatic vein stenosis	Averts need for surgery	High rate of restenosis or shunt occlusion
TIPS	Possible bridge to transplant in fulminant BCS Acute BCS Subacute BCS if portacaval pressure gradient <10 mm Hg or IVC is occluded	Low mortality Useful even with compression of IVC by caudate lobe	High rate of shunt stenosis Extended stents may interfere with liver transplant
Surgical shunt	Subacute BCS Portacaval pressure gradient >10 mm Hg	Definitive procedure for many patients Low rate of shunt dysfunction with portacaval shunt	Risk of procedure-related death Limited applicability Limited availability of surgical expertise
Liver transplant	Fulminant BCS Presence of cirrhosis Failure of portosystemic shunt	Reverses liver disease May reverse underlying thrombophilia	Risk of procedure-related death Need for long-term immunosuppression

Abbreviations: IVC, inferior vena cava; TIPS, transjugular intrahepatic portosystemic shunt.
Adapted from Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. N Engl J Med. 2004 Feb 5;350(6):578-85. Used with permission.

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27

Portal Hypertension–Related Bleeding

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Portal hypertensive bleeding encompasses a spectrum of conditions that include esophageal, gastric, and ectopic varices and portal hypertensive gastrointestinal enteropathy. Esophageal variceal hemorrhage occurs through a combination of increased portal pressure and local factors within the varix itself. Management of esophageal varices includes primary prophylaxis of variceal hemorrhage, treatment of actively bleeding varices, and prevention of variceal rebleeding (secondary prophylaxis). The choice of therapy for primary prophylaxis depends on patient preferences and includes pharmacologic therapy with β-blockers or variceal band ligation, especially if β-blocker therapy fails or the therapy is not tolerated by the patient. Active bleeding is best treated endoscopically. A combination of pharmacologic and endoscopic therapy is preferred for secondary prophylaxis. Surgical shunts or transjugular intrahepatic portosystemic shunts (TIPSs) are second-line therapy. Liver transplant is a treatment option aimed at the underlying cause of portal hypertension but does not have a role in the management of acute bleeding.

Pathogenesis of Portal Hypertension

An increase in the hepatic venous pressure gradient—the difference between the wedged hepatic venous pressure and the free hepatic venous pressure—of at least 10 mm Hg is required for the development of esophageal varices, and a hepatic venous pressure gradient of 12 mm Hg or more is required for the rupture of esophageal varices. Wedged hepatic venous pressures can be measured directly by a transjugular route, but expertise in this procedure is usually available only at large referral centers.

In cirrhosis, portal hypertension occurs through an increase in resistance to portal venous outflow early in the disease process. This increase is due to mechanical factors related to the distortion of liver architecture. However, approximately 30% of the increase in resistance occurs through potentially reversible vascular factors and is the target of pharmacotherapy. Portal hypertension is maintained through the development of a systemic hyperdynamic circulation and peripheral vasodilatation. Physical examination findings in a patient in the hyperdynamic state include relative hypotension and relative tachycardia; a cardiac outflow murmur may be present. The hyperdynamic circulation is characterized in the splanchnic circulation by vasodilatation and increased flow at the level of the splanchnic arterioles. This leads to increased portal venous inflow and exacerbates the existing portal hypertension. Drugs such as octreotide and vasopressin reduce splanchnic hyperemia and portal venous inflow. Portal hypertension results in the development of collateral circulation, which may decrease portal pressure. In addition to esophageal and gastric varices, gastric and intestinal vascular ectasia and portal hypertensive gastropathy occur in patients who have portal hypertension.

Esophageal Varices

Pathogenesis

Local factors that determine the risk of hemorrhage from esophageal varices include the radius of the varix, the thickness of the varix wall, and the pressure gradient between the varix and the esophageal lumen. Factors that determine the severity of bleeding are the degree of liver dysfunction, the severity of the associated coagulopathy, the portal pressure, and the size of the rent in the varix. Endoscopic sclerotherapy or band ligation is an attempt to decrease flow through the varix by inducing thrombosis and, ultimately, to obliterate the varix.

Abbreviation: TIPS, transjugular intrahepatic portosystemic shunt

Therapy

The current recommendations for treatment of esophageal variceal bleeding are summarized in Table 27.1.

Primary Prophylaxis

All patients with cirrhosis should undergo upper endoscopy to screen for the presence and size of esophageal varices. Capsule endoscopy and computed tomography are promising methods for detecting varices but, currently, are not recommended for screening. Varices should be characterized as either small (≤5 mm in diameter) or large (>5 mm in diameter). Large varices are seen in 16% of patients who undergo screening by endoscopy. In approximately 25% of patients with large varices, variceal hemorrhage will develop within the ensuing 2 years. For patients with large varices and advanced liver disease (Child-Pugh class C), the risk of hemorrhage can be as high as 75%. Thus, prophylactic therapy is indicated for patients with large varices. The absence of endoscopic signs that indicate high risk (eg, red wales) does not influence the decision to initiate therapy. Prophylactic treatment may also be considered for patients with Child-Pugh class C status and small varices. If only small varices are detected at endoscopy, the procedure should be repeated in 1 year to assess for progression in size. If no varices are detected at endoscopy, the procedure should be repeated in 2 or 3 years to screen for newly formed varices.

The established primary prophylaxis is treatment with nonselective β-adrenergic blocking agents (β-blockers), such as propranolol and nadolol, or with endoscopic variceal band ligation. It is important to use only nonselective agents rather than β_1-selective agents (eg, metoprolol). β_1-Blockade decreases cardiac output and splanchnic blood flow, whereas the additional β_2-blockade allows unopposed α_1-adrenergic constriction in the splanchnic circulation. This decreases portal blood flow and, consequently, portal pressure. Therapy is started at a low dose, with slow upward titration of the dose until a resting pulse rate of 55 to 60 beats per minute is achieved or hypotension develops (systolic blood pressure <90 mm Hg).

A long-acting preparation of propranolol administered as a single dose in the early evening is preferred. This allows adequate β-blockade at night, when the risk of bleeding is high. With the long-acting preparation administered in the evening, β-blockade is less during the following day, thus decreasing the side effect of fatigue. At the same time, the risk of bleeding is lower during the day, and the lesser degree of β-blockade is not deleterious to the patient.

Carvedilol, a nonselective β-blocker with additional α_1-blocking properties, is another agent that might be used for primary prophylaxis. Nitrates have no place in primary prophylaxis, either when administered as single agents or in combination with β-blockers.

Whenever possible, the hemodynamic response to pharmacologic therapy should be measured. The goal of therapy is to decrease the hepatic venous pressure gradient to less than 12 mm Hg or by 20% when compared with baseline.

Although sclerotherapy is no longer used as a form of primary prophylaxis, variceal band ligation may be an alternative approach to primary prophylaxis because of the lower rate of esophageal ulceration and more effective obliteration of variceal structures than with sclerotherapy. Currently, esophageal variceal ligation is recommended for patients who have contraindications to therapy with β-blockers, who have not had a decrease in the hepatic vein pressure gradient, or who have experienced adverse effects from β-blocker therapy. A meta-analysis of all the studies that compared β-blockers and endoscopic variceal ligation showed no significant difference in mortality risk between the 2 treatments, but participants who underwent variceal ligation had a decreased risk of bleeding. Often, patient preference may be the factor that best determines which therapy is used.

Control of Esophageal Variceal Hemorrhage

Active esophageal variceal bleeding is managed best by endoscopic means, preferably variceal band ligation. After gastrointestinal tract bleeding has been detected in patients with cirrhosis, immediate initiation of pharmacologic therapy is beneficial—even before endoscopy has demonstrated variceal bleeding. Pharmacologic therapy is continued for up to 5 days after endoscopic treatment of varices to reduce the risk of immediate rebleeding. Vasopressin is a potent splanchnic vasoconstrictor that decreases portal venous inflow, thereby decreasing portal pressure, but it is seldom used. Nitroglycerin is used only in conjunction with vasopressin to further decrease portal pressure and reduce the ischemic adverse effects of vasopressin, which are pronounced and limit therapy in up to 30% of patients. Octreotide, a long-acting synthetic somatostatin analogue, is the pharmacologic agent most commonly used. It appears to decrease portal pressure by inhibiting the release of glucagon and the ensuing postprandial hyperemia and by having a direct vasoconstrictive effect on splanchnic arteriolar smooth muscle. Although octreotide is safer than vasopressin, the efficacy of the compound has not been well established. However, a recent meta-analysis has suggested that octreotide is beneficial for acute bleeding. Octreotide is administered as an initial bolus of 50 mcg, followed by an infusion at 50 mcg hourly for 5 days, in conjunction with endoscopic variceal band ligation. β-Blockers should not be used in the presence of acute bleeding, since they will worsen hypotension.

For treating active bleeding, the use of TIPS is limited to patients with refractory bleeding or immediate rebleeding after 2 separate, unsuccessful attempts at endoscopic intervention performed within 24 hours. The use of TIPS is preferred to surgical intervention, particularly in patients with Child-Pugh class B or C status. Since expertise with performing surgical shunts is limited to large referral centers, surgical intervention is impractical for acute bleeding. Also, gastric varices can be obliterated

Table 27.1. Recommendations for Treatment of Esophageal Variceal Bleeding

Type of Treatment	*First-line Therapy*	*Second-line Therapy*	*Other Therapy*
Primary prophylaxis	β-Blockers or endoscopic variceal band ligation		
Control of bleeding	Endoscopy and octreotide (or other vasoactive pharmacologic agents)	TIPS	
Secondary prophylaxis	Endoscopy and β-blockers	TIPS	Liver transplant

Abbreviation: TIPS, transjugular intrahepatic portosystemic shunt.

concomitantly with TIPS placement through the injection of gel foam or coils into the gastroesophageal collateral vessels.

Supportive and resuscitative care includes early elective intubation for airway protection, volume replacement, treatment of coagulopathy, and vigorous surveillance and treatment of concomitant infection. Maintenance of a hematocrit of 25% is appropriate because aggressive transfusion of blood products may precipitate further bleeding by increasing portal pressure. Antibiotic prophylaxis for 7 days with norfloxacin, 400 mg twice daily, is recommended to decrease the incidence of bacteremia and spontaneous bacterial peritonitis, which commonly accompany variceal hemorrhage. Antibiotic therapy is probably the most important reason why the mortality rate of variceal bleeding has decreased from 50% to about 20%. Lactulose therapy may be instituted to treat hepatic encephalopathy. When quinolone resistance is likely, ceftriaxone is administered intravenously in a dose of 1 g every 24 hours.

Secondary Prophylaxis

Secondary prophylaxis involves therapies to prevent rebleeding in patients who have already bled from esophageal varices. Intervention is essential because up to 80% of patients who have already bled from varices will bleed again within 2 years. Treatments include pharmacotherapy with β-blockers, endoscopic band ligation, TIPS, and surgical shunts. Either β-blockers or endoscopic therapy is an appropriate treatment option for patients who did not receive β-blockers for primary prophylaxis. Band ligation is the preferred endoscopic treatment because of the lower incidence of esophageal ulceration and ease of therapy. After acute bleeding has been controlled with variceal ligation, the next ligation session is scheduled in approximately 10 to 14 days. Subsequent sessions are scheduled every 3 to 4 weeks. Varices usually can be obliterated over several weekly sessions. Combination therapy of band ligation and β-blockers is preferred to either treatment used alone.

For patients in whom primary prophylaxis with β-blockers failed, the addition of oral nitrates to the pharmacologic regimen may further decrease portal pressure and the incidence of rebleeding. However, concern remains about the long-term effects of oral nitrates on patient survival; therefore, endoscopic obliteration in combination with β-blockers is currently the preferred approach for secondary prophylaxis for patients in whom primary prophylaxis with β-blockers failed. TIPS should be used only in patients with recurrent or refractory bleeding despite pharmacologic and endoscopic therapies, especially if they are candidates for liver transplant. Although a recent study has suggested benefit to early TIPS placement in patients with acute bleeding, this is not yet widely accepted and there is hesitation in recommending widespread use of TIPS because of the risk of worsening encephalopathy, the potential for liver deterioration, and uncertain effects on long-term survival, particularly of patients with advanced dysfunction of liver synthesis. A surgical shunt should be considered for patients with Child-Pugh class A status and for patients for whom continued medical surveillance will be unlikely, because TIPS requires close ultrasonographic follow-up of the shunt to evaluate for restenosis. However, the rate of TIPS stenosis has decreased with the adoption of covered stents. The use of a surgical shunt depends on the expertise at the institution and on the patient's potential as a candidate for liver transplant. All potential candidates who have variceal hemorrhage should be referred to a transplant center to be evaluated for liver transplant.

Portal Hypertensive Lesions in the Stomach

Gastric lesions that cause portal hypertensive bleeding include gastric varices, portal hypertensive gastropathy, and gastric vascular ectasia. Because no evidence-based management strategies are available for gastric sources of portal hypertensive bleeding, therapy often requires an empirical approach.

Gastric Varices

The most common gastric varices are esophageal varices that extend into the cardia of the stomach and are readily treated with endoscopic techniques such as sclerotherapy or band ligation. The most common sources of gastric variceal bleeding are varices in the fundus of the stomach that are either extensions of esophageal varices or are isolated gastric fundal varices. Recent data have suggested that the frequency of bleeding from gastric varices is similar to that from large esophageal varices. Gastric varices are more likely to be found in patients who have had bleeding from esophageal varices than in those who have not had bleeding. The risk of bleeding from gastric varices is related to the size of the varix, liver function according to the Child-Pugh class, and the presence of red signs on the varix.

β-Blockers are recommended for primary prophylaxis of gastric varices. Acute gastric variceal bleeding is treated best endoscopically. Gastric cardiac varices, like esophageal varices, can be treated with band ligation, while gastric fundal varices are treated best with injection of cyanoacrylate glue. Currently, however, cyanoacrylate glue injection is not readily available in the United States. Other options include sclerotherapy with ethanolamine oleate or thrombin, but the success rate has varied.

Although pharmacologic therapy (eg, β-blockers) may be used to prevent gastric variceal rebleeding, no studies support this practice. The policy at Mayo Clinic generally has been to consider a portosystemic shunt for the prevention of rebleeding in patients with documented gastric fundal variceal bleeding if variceal obturation with cyanoacrylate is not possible. TIPS is used for patients with poor liver function; patients with Child-Pugh class A status should be considered for portosystemic shunt surgery.

Portal Hypertensive Gastropathy

Portal hypertensive gastropathy is a source of gastrointestinal tract bleeding in some patients with cirrhosis and portal hypertension. The elementary lesion is a mosaic-like pattern of the gastric mucosa, but this is not specific. The more specific lesion is the red marking, which may be either a red point lesion less than 1 mm in diameter or a cherry-red spot larger than 2 mm in diameter. The presence of a mosaic-like pattern alone designates mild portal hypertensive gastropathy, whereas red markings superimposed on the mosaic pattern suggest severe portal hypertensive gastropathy. Lesions of portal hypertensive gastropathy tend to be more common in the proximal stomach and in patients who have advanced stages of liver disease according to the Child-Pugh classification, in patients who have esophageal varices, in patients who previously have had esophageal variceal therapy, and in patients who have gastric varices. Approximately 3% of patients who have severe gastropathy may present with acute upper gastrointestinal tract bleeding, and approximately 15% have chronic bleeding.

Anecdotally, acute bleeding from portal hypertensive gastropathy has been treated, with a high success rate, with

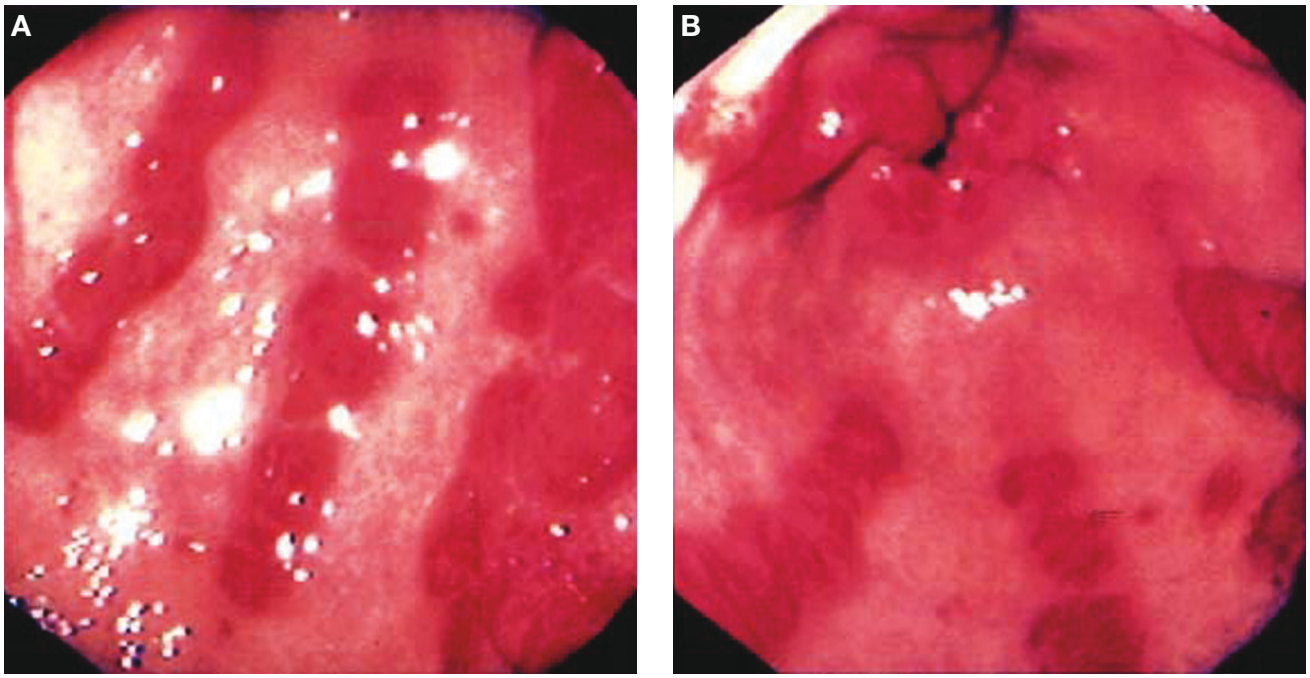

Figure 27.1. Gastric Antral Vascular Ectasia. A and B, Note the linear aggregates of red markings in the antrum and the absence of an underlying mosaic-like pattern.

vasoactive drugs such as vasopressin, somatostatin, and octreotide. Portosystemic shunts should be considered as rescue treatments if vasoactive drug therapy fails. Patients who present with chronic bleeding may be treated with iron supplementation and β-blockers. For these patients, treatment should be continued indefinitely or until liver transplant. Portosystemic shunts may be used as rescue treatment in patients who continue to be transfusion-dependent in spite of adequate β-blocker therapy.

Gastric Vascular Ectasia

A less common gastric mucosal lesion in portal hypertension is gastric vascular ectasia. In contrast to portal hypertensive gastropathy, gastric vascular ectasia is characterized by red markings in the absence of a mosaic-like pattern. The red markings may be arranged in linear aggregates in the antrum, for which the term *gastric antral vascular ectasia* (or watermelon stomach) is used (Figure 27.1). If the red markings do not have a typical linear arrangement, the lesion is designated *diffuse gastric vascular ectasia*. The diffuse lesions also may involve the proximal stomach, sometimes making differentiation from severe portal hypertensive gastropathy difficult. When the diagnosis is uncertain, gastric mucosal biopsy, which usually is safe, may be helpful. Liver dysfunction seems to be necessary for the pathogenesis of vascular ectasia because these lesions may resolve with liver transplant.

Treatment of gastric vascular ectasia is difficult. Some patients may be managed with only iron replacement therapy. β-Blockers do not seem to be effective for these lesions, although controlled trials have not been conducted because of the rarity of gastric vascular ectasia. Thermoablative therapies such as argon plasma coagulation may be tried, but the results are poor, especially for the diffuse form. Cryotherapy may be successful in controlling bleeding in patients with the diffuse variety of vascular ectasia. Antrectomy is effective, but the mortality and morbidity related to the operation can be substantial for patients with cirrhosis. These lesions do not respond to portosystemic shunts, either surgical or TIPS, but occasionally they may respond to estrogen-progesterone combinations (eg, mestranol 50 mg in combination with norethindrone 1 mg daily).

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28

Ascites, Hepatorenal Syndrome, and Encephalopathy

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The portal hypertension and hepatic synthetic dysfunction of cirrhosis cause 3 main complications as liver disease progresses from compensated to decompensated disease: variceal bleeding, ascites, and hepatic encephalopathy (HE). Variceal bleeding is discussed in Chapter 27.

Ascites

Ascites is the most common major complication of cirrhosis and occurs in about 50% of patients with compensated cirrhosis in 10 years. The development of ascites denotes the transition from compensated to decompensated cirrhosis. It causes increased morbidity from abdominal distention and increased mortality from complications such as spontaneous bacterial peritonitis and renal dysfunction, with 15% of patients dying in 1 year and 44% in 5 years.

Pathogenesis of Ascites

Now that the hemodynamic changes in chronic liver disease and portal hypertension are much better understood, there is a greater understanding of the pathogenesis of ascites. Increased hydrostatic pressure within hepatic sinusoids occurs from structural changes due to architectural distortion by fibrosis and nodular regeneration (about 70% of the increase), with 20% to 30% of the increase from increased intrahepatic vascular tone due to vasoactive factors. This increase in hepatic sinusoidal pressure appears to be the primary event that leads to splanchnic (and eventually systemic) vasodilatation, which in turn causes underfilling of the vascular compartment and baroreceptor-mediated stimulation of the renin-angiotensin-aldosterone system, the sympathetic nervous system, and antidiuretic hormone (ADH) release. The net result is the retention of renal sodium and water. Nitric oxide appears to be an important factor in the regulation of intrahepatic vascular tone. Considerable evidence now shows that, in cirrhosis, the decreased availability of hepatic vascular nitric oxide impairs relaxation and increases hepatic perfusion pressure. However, the splanchnic and systemic vasculature exhibit marked overproduction of endothelial nitric oxide, which results in arterial vasodilatation and, subsequently, tachycardia, increased cardiac output, and decreased arterial pressure.

The hepatic sinusoids are a very low-pressure hydrostatic system, compared with other capillary beds (vascular inflow is partly portal venous blood that has a hydrostatic pressure only slightly higher than systemic venous pressure). In addition, with albumin freely diffusible across hepatocyte and endothelial membranes, the oncotic pressure gradient within the sinusoids is very low and does not counteract any increase in hydrostatic pressure. Thus, with portal hypertension, increased pressure in the hepatic sinusoids and splanchnic vessels causes fluid to move into the tissues and to "weep" from the surface of the liver as ascites. A minimum hepatic venous pressure gradient of 10 to 12 mm Hg is necessary for ascites to develop.

Evaluation of Patients With Ascites

The first step in the diagnostic approach to patients with ascites is to determine the cause (Box 28.1). In 85% of cases, ascites is due to cirrhosis and the diagnosis is usually obvious. About 15% of cases are due to nonhepatic causes (malignancy, tuberculosis,

Abbreviations: AASLD, American Association for the Study of Liver Disease; ADH, antidiuretic hormone; CTP, Child-Turcotte-Pugh; MELD, Model for End-stage Liver Disease; PMN, polymorphonuclear neutrophil; HE, hepatic encephalopathy; SAAG, serum-ascites albumin gradient; TIPS, transjugular intrahepatic portosystemic shunt

Box 28.1. Diagnostic and Therapeutic Algorithm for Patients With Ascites

Does the patient have cirrhosis?

If yes, are there any other complications of cirrhosis—spontaneous bacterial peritonitis, portal vein thrombosis, active liver disease, or malignancy?

Prognostic factors for therapy—urinary sodium excretion and renal function

Consideration of therapeutic options

constrictive pericarditis, right-sided heart failure, myxedema, and renal causes), and these must be differentiated from cirrhosis and treated appropriately.

Diagnostic paracentesis is mandatory and should be performed in all patients who present with new-onset ascites, who are hospitalized with cirrhotic ascites, or who have cirrhotic ascites and any deterioration in liver function, with fever, worsening encephalopathy, or renal failure. Because bleeding is uncommon, the routine prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended. In all cases, ascitic fluid analysis should include a blood cell count, with both a total nucleated cell count and a polymorphonuclear neutrophil (PMN) count, and bacterial culture by bedside inoculation of blood culture bottles. Ascitic fluid protein and albumin levels are measured simultaneously with the serum albumin level to calculate the serum-ascites albumin gradient (SAAG). The albumin concentration in ascitic fluid is inversely proportional to portal pressure. In most cases, a SAAG value of 1.1 g/dL or more confirms, with greater than 95% accuracy, the clinical suspicion of portal hypertensive-related ascites. The other main cause for a high SAAG value is portal hypertension related to cardiac failure, but in that case the total protein concentration in the ascitic fluid is usually 2.5 g/dL or more (<2.5 g/dL in cirrhosis-related portal hypertension) (Table 28.1).

Other tests should be performed only if a specific diagnosis is suspected clinically. Lactate dehydrogenase and glucose levels should be determined if secondary peritonitis is suspected. Other tests to consider are amylase (>1,000 U/L suggests pancreatic ascites), cytology (at least at the initial tap), and triglycerides (if the ascitic fluid is cloudy; the concentration is <100 mg/dL in cirrhosis). Mycobacterial culture should be performed only if tuberculosis is strongly suspected. Other ascitic fluid indices (eg, lactate and pH) generally offer little or no additional information. Gram staining is rarely positive.

Table 28.1. Ascitic Protein and Serum-Ascites Albumin Gradient (SAAG)

Total Protein, g/dL	*SAAG, g/dL*	
	≥1.1	*<1.1*
<2.5	Cirrhosis	Nephrotic syndrome
	Acute liver failure	Myxedema
≥2.5	Congestive heart failure	Peritoneal carcinomatosis
	Constrictive pericarditis	Tuberculous peritonitis
	Budd-Chiari syndrome	Pancreatic ascites
	Venoocclusive disease	Chylous ascites

In addition to spontaneous bacterial peritonitis, other cirrhotic complications that may increase ascites, including malignancy, portal or hepatic venous thrombosis, or active liver disease, should be sought with liver tests or imaging studies. Any active liver disease (alcoholic, autoimmune, or hepatitis B) must be treated appropriately. Renal function and renal sodium excretion should be assessed because they are clinical predictors of a therapeutic response: Patients with normal serum urea nitrogen and creatinine levels and sodium excretion of more than 10 mEq/L (without taking diuretics) generally are very sensitive to sodium restriction and diuretic therapy. Patients with marked sodium retention, particularly those with abnormal urea and creatinine levels, require much higher doses of diuretics.

Therapy for Cirrhotic Ascites

Sodium Restriction and Diuretic Therapy

Cirrhotic ascites is perpetuated by renal retention of sodium and water. Therefore, treatment must produce a negative sodium balance. About 10% of patients with cirrhotic ascites have a response to salt restriction alone. Ascites will be controlled in 65% of patients with the initiation of spironolactone therapy and in another 25% with the addition of a loop diuretic. Thus, 90% of patients can be managed, often as outpatients, by the sequential introduction of sodium restriction, generally to 2 g daily (88 mEq), and then diuretic therapy.

Spironolactone, an aldosterone antagonist, is an effective diuretic in most patients who have nonazotemic cirrhosis with ascites and is more effective than furosemide for single-agent therapy. Combination therapy with furosemide is used more generally to achieve a more rapid natriuresis and to maintain normokalemia. Spironolactone is given at an initial dose of 100 mg daily, with increases in 100-mg increments as appropriate to 400 mg daily, according to the clinical response and adverse effects (particularly hyperkalemia). Furosemide usually is started at a dose of 40 mg daily in combination with spironolactone and increased in 40-mg increments to 160 mg daily until the desired effect is achieved or adverse effects occur.

Diuretic therapy is titrated to achieve optimal weight loss without complications—that is, 1) deterioration in renal function, 2) excessive weight loss in relation to ascites or edema, 3) orthostatic symptoms, 4) encephalopathy, or 5) dilutional hyponatremia unresponsive to fluid restriction. Generally, a daily weight loss of 0.5 to 1.0 kg is optimal to avoid adverse effects because only 750 to 900 mL of fluid can be mobilized daily from the abdomen into the general circulation. After the fluid is mobilized by whatever method, diuretic therapy should be adjusted to keep the patient free of ascites. The role of selective vasopressin V2 receptor antagonists (eg, tolvaptan) in the management of ascites with or without hyponatremia remains to be defined.

Therapeutic Paracentesis

In randomized studies of patients with tense ascites and avid sodium retention, repeated large-volume paracentesis (with intravenous infusions of albumin), compared with diuretic therapy, is 1) more effective in eliminating ascites; 2) associated with a lower incidence of hyponatremia (5% vs 30%), renal impairment (3.4% vs 27%), and HE (10.2% vs 29%); and 3) associated with shorter hospital stay and reduced cost of therapy without any differences in survival, spontaneous bacterial peritonitis, or causes of death.

Intravenous infusion of 25% albumin is an important measure to prevent circulatory dysfunction in patients with cirrhosis and tense ascites who are treated with large-volume (>5 L) or total paracentesis. Complete mobilization of ascites without plasma volume expansion causes a deterioration in systemic hemodynamics in all patients; in 20%, hyponatremia or renal dysfunction develops, which is frequently irreversible. Generally, 8 g of albumin is infused for every 1 L of ascitic fluid removed. Dextran 70 and polygeline are less effective than albumin as plasma volume expanders and are not recommended. Terlipressin may be an alternative to albumin, but it is not available in the United States.

Drugs to Avoid in Cirrhotic Ascites

Nonsteroidal antiinflammatory drugs are contraindicated and aminoglycosides are generally avoided if there are effective alternative antibiotics. Drugs that decrease arterial pressure or renal blood flow should be avoided (eg, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and α-adrenergic blockers). Pharmacologic acid suppression may increase the incidence of spontaneous bacterial peritonitis in cirrhotic ascites.

Refractory Ascites

Definition

Refractory ascites is due to avid renal retention of sodium and occurs in about 10% of patients with decompensated cirrhosis. Clinically, ascites is considered to be refractory when a patient has adequate sodium restriction and receives maximal tolerable doses of diuretics but does not lose the desired weight (ie, 24-hour urine sodium is less than intake). Patients who have not had a response to spironolactone 400 mg daily and furosemide 160 mg daily have *diuretic-resistant ascites*. Ascites is termed *diuretic-intractable* when therapy is prevented by diuretic complications. Reversible factors that contribute to sodium retention should be identified and corrected (Box 28.2).

Treatment Options

The long-term prognosis after the development of refractory ascites is dismal, with a high 1-year mortality rate (>70%). Liver transplant is the only therapy capable of improving both quality of life and patient survival. Consequently, liver transplant should always be considered for an otherwise acceptable candidate with ascites that cannot be controlled with adequate sodium restriction and diuretic therapy.

Until a patient undergoes liver transplant or if a patient cannot undergo liver transplant, therapeutic options for refractory ascites are limited to repeated therapeutic (large-volume or total) paracentesis or a transjugular intrahepatic portosystemic shunt (TIPS). According to the treatment recommendations of the American Association for the Study of Liver Diseases (AASLD), first-line therapy for refractory ascites is therapeutic paracentesis, and TIPS is reserved for patients who cannot tolerate paracentesis or who require large-volume paracentesis for refractory ascites for more than 2 or 3 months. Peritoneovenous shunting may be considered as a last resort for patients who are not candidates for repeated large-volume paracentesis, liver transplant, or TIPS. Diuretic therapy should be discontinued in refractory ascites when urine sodium excretion is less than 30 mmol daily. Consideration may be given to discontinuation of β-blocker therapy, if possible, since it may increase the risk of paracentesis-induced circulatory dysfunction.

Box 28.2. Reversible Factors for Lack of Response to Diuretic Therapy in Cirrhotic Ascites

- Inadequate sodium restriction
- Inappropriate use of diuretics
- Nephrotoxic medications
- Spontaneous bacterial peritonitis
- Portal or hepatic vein thrombosis
- Untreated active liver disease

TIPS in Refractory Ascites

The hemodynamic effects of TIPS have been well described. Increased cardiac output and a further decrease in systemic vascular resistance occurs temporarily for 1 to 3 months, but increased urinary excretion of sodium starts from 7 to 28 days after the procedure, together with a decrease in plasma renin activity and aldosterone levels. Resolution of ascites is slow, and diuretic therapy should be continued initially.

Five randomized trials with 330 patients have shown that TIPS is effective in reducing ascites in about 50% of patients at the expense of a 20% higher incidence of encephalopathy. Overall patient survival is unchanged by TIPS, but in some patients, liver function deteriorates significantly. TIPS is relatively contraindicated for patients who are older than 70 years, have cardiopulmonary dysfunction, renal failure or advanced liver disease; mortality increases for patients with a pre-TIPS Child-Turcotte-Pugh (CTP) score greater than 11 or a Model for End-stage Liver Disease (MELD) score greater than 14. Survival after TIPS for refractory ascites is less than survival after TIPS for variceal bleeding. Predictors of worsening encephalopathy are age older than 65 years, pre-TIPS encephalopathy, or a TIPS gradient less than 5 mm Hg. The use of expanded polytetrafluoroethylene-covered stents is now preferred to bare stents because of less shunt dysfunction and perhaps better survival. However, the optimal hepatic venous pressure gradient for control of ascites is not known.

Hepatic Hydrothorax

Hepatic hydrothorax is a complication of cirrhotic ascites in 5% to 10% of patients. Management is the same as for ascites, with sodium restriction and diuretic therapy. TIPS is effective in some patients. Thoracentesis is recommended only if the diagnosis is uncertain, if infection is strongly suspected, or for symptomatic relief. Chest tubes and pleurodesis should be avoided.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis is an infection of ascitic fluid without a known source of infection. It occurs in 10% to 30% of patients with cirrhotic ascites and is frequently recurrent (70% recurrence rate in 1 year). In the past, the infecting organisms were normal bowel flora, with 70% of cases caused by gram-negative bacilli (especially *Escherichia coli* and *Klebsiella*) and 30% by gram-positive cocci (mainly *Streptococcus* and *Enterococcus* species), with anaerobes

being very uncommon (<5% of cases). Most infections (92% of cases) are caused by a single organism, and 8% are polymicrobial. The era of norfloxacin prophylaxis has caused epidemiologic changes in bacterial flora, with a shift toward more gram-positive infections. Intestinal bacterial translocation generally is considered the main pathogenic mechanism leading to spontaneous bacterial peritonitis, by which bacteria move from the gut to mesenteric lymph nodes and, hence, into the systemic circulation before infecting the peritoneal cavity.

The clinical presentation and severity of spontaneous bacterial peritonitis are extremely variable, from chills, fever, and abdominal pain to no symptoms. The diagnosis may be missed unless paracentesis is performed. Often, the clinical picture consists of a single feature, such as fever, abdominal pain, hypothermia, hypotension, diarrhea, lack of response to diuretics, deterioration in renal function, or worsening portosystemic encephalopathy. Patients with cirrhosis who are at particular risk for spontaneous bacterial peritonitis are those with more advanced cirrhotic-stage liver disease, a low concentration of ascitic fluid protein (<1 g/dL), bilirubin level higher than 3.2 mg/dL, or gastrointestinal tract hemorrhage. Renal impairment is common in these patients and a clinical predictor of poor outcome.

Diagnosis

Ascitic fluid analysis is essential for the diagnosis of spontaneous bacterial peritonitis (Figure 28.1). However, the clinical presentation of this condition can be subtle and easily missed clinically. Diagnostic paracentesis should be performed in all patients hospitalized with cirrhotic ascites and in patients who present with signs of infection, encephalopathy, deterioration of renal function, or gastrointestinal tract bleeding. Bedside inoculation of blood culture bottles with 10 mL of ascitic fluid is essential for maximizing the likelihood of positive cultures.

A presumptive diagnosis of spontaneous bacterial peritonitis is made if the ascitic fluid has more than 250 PMNs per milliliter in a patient with cirrhotic ascites and no secondary source of infection. Blood cultures are performed before starting antibiotic therapy. Confirmation is by positive bacterial culture of the ascitic fluid; if the bacterial culture is negative, the diagnosis of culture-negative neutrocytic ascites is made if there is no recent history of antibiotic therapy and no other cause of neutrocytic ascites (cholecystitis, pancreatitis, hemorrhage, recent abdominal surgery, or carcinomatosis). Patients with culture-negative neutrocytic ascites have clinical and biochemical features identical

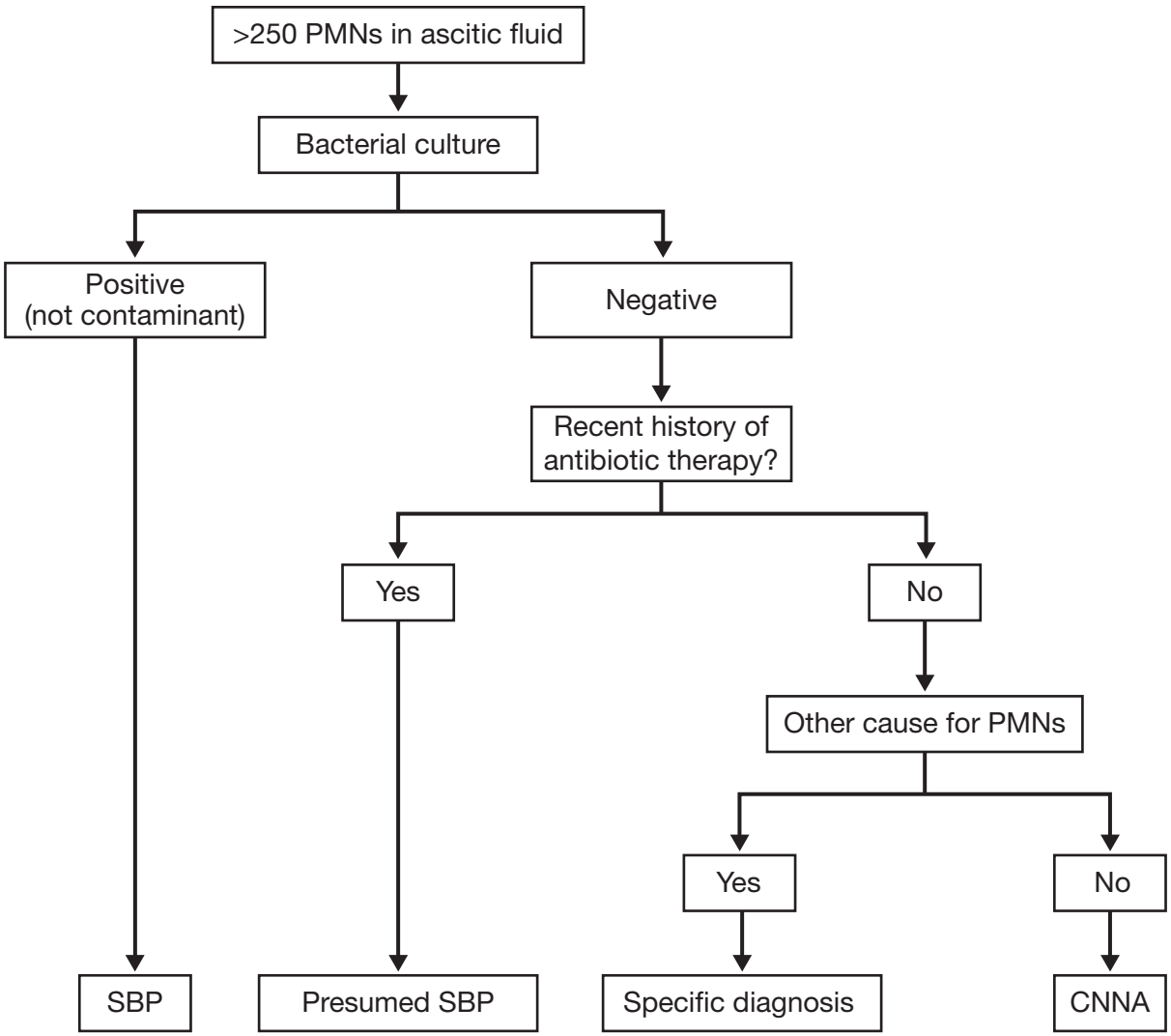

Figure 28.1. Diagnostic Algorithm for Spontaneous Bacterial Peritonitis (SBP). CNNA indicates culture-negative neutrocytic ascites; PMN, polymorphonuclear neutrophil.

to those with microbiologically confirmed spontaneous bacterial peritonitis, and they are assumed to represent cases of spontaneous bacterial peritonitis missed with current culture techniques. Bacterascites is defined by ascitic fluid that contains fewer than 250 PMNs per milliliter and a positive bacterial culture. It is usually the transient residence of bacteria in the ascitic fluid. Patients with bacterascites generally have less severe liver disease than those with spontaneous bacterial peritonitis. Although bacterascites may progress to spontaneous bacterial peritonitis, it usually clears spontaneously without antibiotic therapy.

Treatment

Antibiotic Therapy

With the finding of a high PMN count in ascitic fluid, empirical therapy for spontaneous bacterial peritonitis must be instituted and directed against aerobic enteric bacteria. Cefotaxime, 2 g intravenously every 8 hours, is the first choice of antibiotic for empirical therapy and is started when the PMN count in ascitic fluid is more than 250 cells per milliliter. This therapy is more effective (86%) than an ampicillin-aminoglycoside combination and is associated with less renal toxicity in patients with cirrhosis. Aztreonam is less effective because of its lack of activity against gram-positive organisms; parenteral amoxicillin-clavulanic acid and quinolones have been found to be clinically effective. After the organism has been identified, antibiotic therapy can be adjusted accordingly. Uncomplicated spontaneous bacterial peritonitis, in patients not already receiving quinolones, may be treated effectively in an outpatient setting with oral ofloxacin, a much less expensive alternative. Patients with an ascitic fluid PMN count less than 250 cells per milliliter but with signs of infection (fever, abdominal pain, or tenderness) should receive antibiotic therapy while awaiting culture results.

Epidemiologic changes in bacterial infections have occurred with norfloxacin prophylaxis, and these must be considered for each patient. A recent study of bacterial infections in patients with cirrhosis who receive norfloxacin prophylaxis has shown that currently 53% of infections are due to gram-positive cocci, especially in nosocomial infections with invasive procedures and in patients in intensive care units. In 50% of patients receiving norfloxacin prophylaxis and in 16% of those not receiving prophylaxis, spontaneous bacterial peritonitis is caused by quinolone-resistant gram-negative bacilli; these organisms often are resistant also to trimethoprim-sulfamethoxazole therapy.

Albumin Infusions

About 30% of patients with cirrhosis who have spontaneous bacterial peritonitis develop renal impairment, an important predictor of mortality for these patients. A randomized trial has shown that albumin infusion on day 1 (1.5 g/kg) and day 3 (1 g/kg) prevented this complication; a recent meta-analysis of 4 randomized trials (288 patients) confirms that albumin infusion prevents acute kidney injury and reduces mortality. AASLD Practice Guidelines state that albumin infusions should be reserved for very ill patients who are most at risk (ie, serum creatinine >1 mg/dL, serum urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL).

Repeated Paracentesis

Diagnostic paracentesis after 48 hours of antibiotic therapy in a recovering patient is often considered unnecessary. However, repeated paracentesis is mandatory for patients who do not show clinical improvement. If the PMN count is greater than the baseline, the patient must be reexamined carefully for secondary sites of infection, including repeated abdominal radiography for free air, computed tomography of the abdomen, and surgical consultation.

Differential Diagnosis

The main differential diagnosis for spontaneous bacterial peritonitis is secondary bacterial peritonitis (5%-10% of cases of bacterial peritonitis in patients with cirrhosis), most commonly from a perforated viscus or occasionally an abscess. Secondary bacterial peritonitis appears to be a chance occurrence but is suspected in patients with liver disease less severe than those with spontaneous bacterial peritonitis. The operative mortality rate for patients with cirrhosis who have infected ascites is about 85%, but for patients with secondary bacterial peritonitis who do not have surgery, mortality is 100%.

Spontaneous bacterial peritonitis and secondary bacterial peritonitis cannot be distinguished on the basis of clinical features. Factors that suggest a secondary infection are a high leukocyte count in ascites (>10,000/mL), multiple or unusual organisms (fungi or anaerobes) in ascitic fluid culture, ascitic fluid protein less than 1 g/dL, glucose level less than 50 mg/dL, lactate dehydrogenase level more than the upper limit of the reference range for serum, and an increase in the number of PMNs in ascitic fluid despite antibiotic therapy. Radiologic imaging is mandatory.

Primary Prophylaxis

Episodes of bleeding in patients with CTP class C cirrhosis or recurrent bleeding in patients with cirrhosis are factors that predict infection and spontaneous bacterial peritonitis, which are often severe. Intravenous ceftriaxone is the prophylactic antibiotic of choice and should be given for 7 days to all patients with advanced cirrhosis who have an episode of gastrointestinal tract bleeding. Patients with less severe liver disease and bleeding may receive an oral quinolone. Long-term oral antibiotic prophylaxis is recommended also for patients with cirrhosis who have very low ascitic fluid protein levels (<1.5 g/dL), especially if they also have a serum creatinine level of 1.2 mg/dL or more, serum urea nitrogen 25 mg/dL or more, serum sodium level 130 mEq/L or less, or a CTP score of 9 or higher with a bilirubin level of 3 mg/dL or more.

Secondary Prophylaxis

Because spontaneous bacterial peritonitis has a 1-year recurrence rate of more than 50%, prophylactic measures are warranted for patients who have survived an episode of this condition. Rarely can the underlying liver disease be treated (except with liver transplant), and only occasionally does diuretic therapy completely clear the ascites. Treatment with norfloxacin, 400 mg daily, can be used to eliminate the gram-negative flora (and reduce gram-negative infection), but it will not affect the other aerobic and anaerobic flora. Trimethoprim-sulfamethoxazole and ciprofloxacin also have been effective for prophylaxis. Daily dosing is preferable to intermittent dosing.

Bacterascites

When diagnostic paracentesis shows no evidence of neutrocytic ascites (PMNs <250/mL) but the ascitic fluid culture grows organisms that are not contaminants, the diagnosis is bacterascites. Paracentesis should be repeated and a decision about therapy based on the following: 1) if PMNs are more than 250/mL, treat as spontaneous bacterial peritonitis; 2) if PMNs are fewer than 250/mL but

again culture-positive, treat with antibiotics; and 3) if PMNs are fewer than 250/mL but cultures are negative, do not treat.

Renal Function Abnormalities in Cirrhosis and Hepatorenal Syndrome

Renal dysfunction is a common complication of cirrhosis, is frequently progressive and severe, and is an important predictor of mortality, especially in patients developing acute kidney injury subsequent to hospitalization. In 1 series, about half of all patients had volume-responsive prerenal azotemia, with acute tubular necrosis in 32% and hepatorenal syndrome in 20%. Infection is a common precipitant in many patients. The hemodynamic changes in chronic liver disease increasingly worsen, with the progression from compensated cirrhosis to ascites (with a high incidence of acute kidney injury) to hepatorenal syndrome. Mild to severe sodium retention by the kidneys, mainly due to increased tubular resorption of sodium, is a key factor in the pathogenesis of ascites formation in cirrhosis. This occurs with activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system and increased secretion of ADH. As liver disease worsens, the activity of the renin-angiotensin-aldosterone and sympathetic systems increases and the secretion of ADH increases. The increased secretion of ADH eventually impairs water excretion, resulting in increased total body water and dilutional hyponatremia. Splanchnic vasodilatation also continues to increase as liver disease worsens. As ascites progresses to type 2 hepatorenal syndrome, extrasplanchnic vasoconstriction begins to affect blood flow to the kidneys, brain, liver, and adrenals. Cardiac output increases in cirrhosis, but eventually as hemodynamic changes worsen, cardiac output decreases due to cirrhotic cardiomyopathy with systolic and diastolic dysfunction, further worsening the blood flow to extrasplanchnic organs and potentiating renal impairment through the renal vasoconstriction of hepatorenal syndrome.

Hyponatremia

The severity of water retention varies considerably from patient to patient, but dilutional hyponatremia occurs in about 30% of hospitalized patients with cirrhotic ascites and is associated with increased morbidity and mortality. However, symptoms are rare until sodium levels are very low (<110-115 mEq/L). Treatment is fluid restriction and should be implemented for serum sodium levels less than 125 mEq/L. Rarely do patients need infusion of hypertonic (3%) saline, and this is administered only to patients with severe, symptomatic hyponatremia. The vaptans are new aquaretic drugs (selective vasopressin V2 receptor antagonists) and may be considered for severe hypervolemic hyponatremia. Oral tolvaptan is now available and causes marked increases in renal water excretion and serum sodium levels. It must be started when the patient is in the hospital with close monitoring and slow titration of the dose to avoid a rapid increase in serum sodium; fluid restriction is avoided and doses of other diuretics are adjusted accordingly. The safety and efficacy of long-term tolvaptan use are undefined.

Major Diagnostic Criteria for Hepatorenal Syndrome

The International Club of Ascites proposed that all the following major criteria must be present for the diagnosis of hepatorenal syndrome:

- Cirrhosis with ascites
- Serum creatinine level more than 1.5 mg/dL
- No improvement after 2 days of diuretic withdrawal and plasma volume expansion with albumin (100 g daily)
- Absence of shock
- No current or recent nephrotoxic drugs or vasodilators
- Absence of parenchymal kidney disease, with proteinuria of less than 500 mg per day; no ultrasonographic evidence of obstructive uropathy or microhematuria

In most cases, the diagnosis is made on the basis of the serum creatinine level, which is a specific but relatively insensitive index of renal function in this setting. Additional diagnostic criteria, which may help in making the diagnosis but are not considered essential, are low urine volume (<500 mL daily), low urine sodium level (<10 mEq/L), urine osmolality greater than plasma osmolality, few urine erythrocytes (<50 per high-power field), and low serum sodium level (<130 mEq/L).

Hepatorenal Syndrome Types 1 and 2

Type 2 hepatorenal syndrome is moderate renal failure that is stable over a long time, and the main consequence is refractory ascites; the creatinine level is stable at 1.5 to 2.5 mg/dL, generally with an increase of less than 0.5 mg/dL daily. In comparison, type 1 hepatorenal syndrome is rapidly progressive renal failure. It usually occurs in patients with type 2 hepatorenal syndrome and results from a precipitating factor such as infection or gastrointestinal tract bleeding. The creatinine level is greater than 2.5 mg/dL or creatinine is more than 1.5 mg/dL, with an increase of 0.5 mg/dL or more daily.

Treatment

Prevention

Renal dysfunction in cirrhotic ascites is more easily avoided than treated. All factors that may potentiate renal dysfunction are avoided, including nephrotoxic drugs (especially nonsteroidal antiinflammatory drugs and aminoglycosides), excessive use of diuretics or lactulose, and large-volume paracentesis without intravenous albumin. Complications such as bacterial infection, gastrointestinal tract bleeding, dehydration, or hypotension must be treated aggressively. Spontaneous bacterial peritonitis should be treated with antibiotics and intravenous albumin. Sepsis is a strong risk factor for acute kidney injury in cirrhosis and is associated with arterial underfilling and renal vasoconstriction. To reduce the risk of hepatorenal syndrome, norfloxacin is recommended for patients with low-protein ascites and CTP score of 9 or higher, bilirubin level 3 mg/dL or more, serum creatinine level 1.2 mg/dL or more, or serum sodium level 130 mEq/L or less.

Therapy

The only therapy proven effective for hepatorenal syndrome is liver transplant. In type 2 hepatorenal syndrome, discontinuation of diuretics and plasma volume expansion are usually effective, at least temporarily. Ongoing use of β-blockers for prophylaxis against variceal bleeding is controversial, but increasing evidence supports their discontinuation. In established type 1 hepatorenal syndrome, patients should undergo plasma volume expansion with albumin to a normal central venous pressure, ideally with central venous pressure monitoring. A further fluid challenge may be tried but usually will be ineffective. These patients require an expedited referral for liver transplant.

There is increasing evidence for the efficacy of vasoconstrictor therapy in combination with plasma volume expansion with

albumin (generally a 100-g initial dose, followed by 20-40 g daily) for type 1 hepatorenal syndrome. Terlipressin is the most widely studied drug, is safe, and has been administered in doses of 0.5 mg every 4 hours, up to 12 mg daily, to more than 154 patients in 2 randomized controlled trials, with a response rate of 50% to 60%. Response to terlipressin is more likely when the bilirubin level is less than 5 mg/dL and there is an early sustained increase in arterial pressure with therapy. However, this drug is not available in the United States. α_1-Adrenergic agonists (midodrine or norepinephrine) also have been used with some benefit with albumin, although there have been no randomized trials. In a small number of patients, midodrine and octreotide have successfully reversed the renal failure. Therapy for hepatorenal syndrome should be introduced as soon as the diagnosis is suspected, before the creatinine is significantly elevated or urine output low.

The condition of a small number of patients with hepatorenal syndrome has improved after TIPS but, in line with AASLD guidelines, controlled trials are required before this treatment can be recommended. Renal replacement therapy, either hemodialysis or continuous venovenous hemofiltration, is used, especially in patients awaiting liver transplant.

Hepatic Encephalopathy

HE is a debilitating complication of cirrhosis for which therapies are still very limited and nonspecific. Furthermore, no weight is given for this complication in the MELD system for organ allocation, resulting in considerable morbidity for patients and a burden for families and the health care system.

In chronic liver disease, noxious substances, presumed nitrogenous compounds from protein breakdown, are ineffectively detoxified or bypassed (or both) by the diseased liver and affect the brain, causing HE, a neuropsychiatric syndrome. The pathophysiologic mechanism is not well understood, but ammonia is regarded to be of central importance.

Clinical Features

HE is a constellation of neuropsychiatric features (dominated by significant psychomotor slowing) that fluctuate greatly over time and range from a trivial impairment in cognition to frank confusion, drowsiness, and coma.

The 4 stages of overt HE (West Haven criteria) are well known:

- Grade 1—Confused; altered mood or behavior; psychometric defects
- Grade 2—Drowsy; inappropriate behavior
- Grade 3—Stuporous but with inarticulate speech and able to obey simple commands; marked confusion
- Grade 4—Coma; unable to be roused

For patients with advanced coma (grade 3 or 4), the Glasgow Coma Scale allows more accurate assessment of progression. Patients with cirrhosis who have no overt HE can be classified as those with normal cognitive function and those with minimal HE characterized by changes in psychomotor speed, visual perception, and attention. Studies have shown that even minimal HE can greatly affect a patient's functioning both at home and at work; recent evidence confirms attention deficit, impaired driving skills with an increased accident rate, and increased risk of falls with significant morbidity.

No laboratory test can confirm the diagnosis, which rests on typical neuropsychiatric features in patients with established chronic liver disease. Other causes of encephalopathy in patients with cirrhosis must be excluded. In difficult cases, magnetic resonance imaging of the head is useful to identify alternative diagnoses, and imaging of the portosystemic circulation may identify large portosystemic shunts.

Neuropsychometric testing is necessary to diagnose minimal HE, which is particularly important for patients at risk of accidents, and may be useful to monitor cognitive decline in low-grade HE. But there is no consensus about the many different tests that assess different domains of cognitive function. Testing may include paper-pencil psychomotor tests (eg, number connection tests), computerized psychomotor tests (eg, inhibitory control test), and neurophysiologic performance tests (eg, critical flicker frequency, mismatch negativity analysis, and electroencephalography). The psychometric hepatic encephalopathy score combines clinical impression with neuropsychologic performance and may prove more sensitive than the West Haven criteria. Asterixis is a nonspecific clinical sign, which generally, but not invariably, occurs in the early stages of HE. Although asterixis is associated with an increased arterial level of ammonia, there is no correlation between the degree of encephalopathy and the ammonia level. Recent studies have suggested that electroencephalographic alterations are associated with severity of liver disease and HE.

Management

Identification of Precipitants

To treat HE and to avoid precipitants of HE in patients who have advanced cirrhosis, the following general measures must be considered:

1. Avoid analgesics, sedatives, and tranquilizers.
2. Control gastrointestinal tract bleeding and purging of blood from the gastrointestinal tract.
3. Screen, and initiate early, aggressive therapy for any infection; this is especially important in advanced coma.
4. Correct acidosis, alkalosis, hypoxia, or electrolyte abnormalities, especially hyponatremia.
5. Prevent constipation and intravascular volume depletion; dehydration secondary to aggressive diuretic or lactulose therapy is a common precipitant. Diuretics must be stopped, and albumin infusion has been found to be beneficial.
6. Ensure adequate intake of glucose to treat hypoglycemia and prevent endogenous protein breakdown.
7. Correct nutritional deficiencies, and provide adequate vitamin supplementation, including thiamine and folate.

Treatment

Lactulose. Lactulose is the mainstay of therapy for most patients for treatment of an acute episode; it has been shown to reduce the recurrence of HE. Lactulose is a nonabsorbable synthetic disaccharide metabolized by colonic bacteria to organic acids. It decreases the absorption of ammonia by acting as an osmotic laxative and also by altering colonic pH. The starting dose is 30 mL 2 or 3 times daily, titrated to produce 2 to 4 stools daily. In comatose patients, lactulose is given by feeding tube or rectally. Excessive therapy can cause dehydration and hypernatremia. Lactitol is equivalent to lactulose but is not available in the United States. Lactulose is effective in lactase-deficient patients.

Antibiotics. Rifaximin is a minimally absorbable antibiotic with broad-spectrum antimicrobial activity which presumably modulates the bacterial flora. It has shown efficacy in the treatment of HE, and multicenter randomized controlled trials have shown that, at doses of 550 mg twice daily (with lactulose in many patients), it reduced the risk of recurrent episodes of

HE better than lactulose alone. In 2 small randomized trials of patients with minimal HE, rifaximin improved driving simulator performance in 1 trial and psychometric testing in the other. It is as effective as, and safer than, neomycin or metronidazole. Neomycin can be absorbed to some extent (1%-3%) and lead to ototoxicity and nephrotoxicity.

Dietary Protein Restriction. Theoretically, increased protein intake increases HE, but less than 10% of HE cases are associated with increased protein ingestion, and some studies have shown improvements in HE in patients with better nutritional status and increased protein intake. Most patients with HE do not need protein restriction. In advanced coma, protein may be withheld for a short time while an adequate level of glucose maintained with intravenous infusion; the precipitating cause for the HE can then be identified and lactulose therapy initiated. It is critical in the long term, however, to maintain a positive nitrogen balance in these patients, particularly if they already have muscle wasting. However, a small subset of patients appears to be "protein sensitive"—that is, they become encephalopathic with moderate amounts of protein. These patients must be given the least amount of protein necessary to maintain a positive nitrogen balance. Protein intake of 1.0 to 1.2 g/kg (based on ideal or dry weight) is essential. Protein is best tolerated if the amount is distributed evenly throughout the day rather than given in large doses. Also, the composition of the protein may make a difference: Vegetable proteins may be more beneficial (less ammoniagenic) than animal proteins. Furthermore, toxicity increases among animal proteins in ascending order as follows: dairy proteins, fish proteins, meat proteins, blood proteins (red meat). Despite no proven clinical benefit in trials, some patients appear to tolerate preparations of branched-chain amino acids better than other proteins. Nevertheless, for patients who are transplant candidates, mild HE is tolerated better in the long term than a negative protein balance. For nontransplant candidates with end-stage liver disease and refractory HE, quality-of-life issues predominate with regard to diet.

Therapies of Indeterminate Efficacy. Zinc is a cofactor of urea cycle enzymes, and its deficiency is implicated in HE. Trials of zinc therapy in HE have been inconclusive, but therapy benefits some patients. Substrate for urea and glutamine synthesis (the 2 major routes of ammonia clearance) is provided by L-ornithine-L-aspartate, which lowers plasma ammonia and improves HE in patients with cirrhosis. Ammonia levels are reduced by sodium benzoate and phenylacetate, and some studies have shown benefit in HE; however, limitations of their use have prevented US Food and Drug Administration approval for HE. Probiotics, especially with lactobacilli and bifidobacteria, have shown some efficacy in HE, but their therapeutic role has not been defined.

Portosystemic Encephalopathy After TIPS. Most post-TIPS HE is maximal during the first 3 months and can be controlled by the above measures. About 8% of cases are refractory to medical treatment; the options are liver transplant and occluding the stent or decreasing its diameter. Stent manipulation is not without morbidity (recurrent variceal bleeding, ascites, and even death) and should be considered only for severely refractory cases. Decreasing the diameter of the stent is safer than occluding it.

Liver Support Devices. The Molecular Adsorbent Recirculating System (MARS; Gambro) has been used recently to treat patients who have acute decompensation of cirrhosis and HE. A US multicenter trial showed that the treated patients had earlier and more frequent improvement in HE but no benefit on mortality.

Liver Transplant. Liver transplant is the ultimate therapy for HE. HE, which is recurrent or difficult to treat, is but one manifestation of a deteriorating liver and is an indication to consider orthotopic liver transplant. Because HE is not linked directly to mortality in cirrhosis, its presence carries no weight over bilirubin, creatinine, and the international normalized ratio in the MELD system for organ allocation.

HE and Spontaneous Portosystemic Shunts. Large spontaneous portosystemic shunts have been identified in some patients with recurrent or persistent HE out of proportion to the severity of their liver disease. These shunts may be amenable to embolization with improvement in HE, and the results of a multicenter survey of the efficacy of this approach are pending.

Prognostic Indicators of Survival in Cirrhosis

Cirrhosis can be considered to have 4 stages. Stage 1 is completely compensated cirrhosis without varices or ascites; the 1-year mortality rate is very low, and about 11% of patients annually have progression to a higher stage. Stage 2 is also compensated, but varices are present without ascites; the mortality rate is a little higher than for stage 1 and 10% of patients have progression to a higher stage. Stage 3 is defined by the presence of ascites, with or without varices; the mortality rate is 20%, with 7% of patients developing bleeding varices. Stage 4 is defined by bleeding varices; it has the highest mortality rate. Both CTP and MELD scores predict mortality.

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29

Metabolic Liver Disease[a]

WILLIAM SANCHEZ, MD

Metabolic liver disease refers to inherited disorders of metabolism that manifest prominently with liver disease. The 3 major inherited disorders that cause liver disease in adults are alpha$_1$-antitrypsin (A1AT) deficiency (A1ATD), Wilson disease, and hereditary hemochromatosis. All are multisystem disorders that cause liver injury by various mechanisms but which can ultimately lead to cirrhosis and complications of liver failure. Also, various inborn errors of metabolism that cause liver disease manifest during childhood (Box 29.1). These inborn errors of metabolism are, in aggregate, a major indication for pediatric liver transplant. As an increasing number of patients with childhood syndromes with liver involvement survive into adulthood, gastroenterologists who treat adults will need to become familiar with their care; however, the childhood syndromes rarely manifest initially in adulthood.

Alpha$_1$-Antitrypsin Deficiency

A1ATD is an inherited disorder characterized by the development of liver disease or lung disease (or both) in children and adults. Clinical manifestations include cirrhosis and emphysematous obstructive lung disease. The presence of emphysema—especially among nonsmokers—in conjunction with chronic liver disease should prompt an evaluation for A1ATD.

Inheritance and Gene Function

A1AT is a member of the serine protease supergene family. The function of A1AT is to protect tissues from the proteolytic activity of serum proteases such as neutrophil elastase. The *A1AT* gene is located on the long arm of chromosome 14.

A1ATD is inherited as an autosomal codominant disorder. This deficiency is characterized on the basis of phenotype rather than genotype. The normal protein is labeled *M*, and abnormal phenotypes include *S, Z*, and *null*. Phenotypes are reported as the combination of alleles present; therefore, the wild-type phenotype is Pi*MM (*Pi* indicates protease inhibitor), and abnormal phenotypes include Pi*MZ, Pi*SS, and Pi*ZZ.

For liver disease, the *Z* phenotypes are the most clinically relevant. The normal Pi*MM phenotype is present in 95% of the population and is associated with normal serum levels of A1AT. Patients with the Pi*MZ phenotype have an intermediate deficiency, and patients with Pi*ZZ have a severe deficiency. The *Z* allele has a heterozygote frequency of 1:30 (Pi*MZ) and a homozygote frequency of 1:2,000 (Pi*ZZ).

Pathophysiology

It is important to recognize that A1ATD causes disease by different mechanisms in the lung and liver. Pulmonary disease is caused by unopposed activity of neutrophil elastase and other proteolytic enzymes that produce tissue damage. In contrast, in the liver, A1ATD is a storage disease. The abnormally folded A1AT protein is unable to be exported from hepatocytes into the circulation. This results in the accumulation of globules of A1AT in the endoplasmic reticulum of hepatocytes, resulting in cell injury and death.

[a] David J. Brandhagen, MD (deceased), John B. Gross Jr, MD, and John J. Poterucha, MD, are gratefully acknowledged as authors of this chapter in the previous editions of the book (parts of which appear in this edition).

Abbreviations: A1AT, alpha$_1$-antitrypsin; A1ATD, alpha$_1$-antitrypsin deficiency; UNOS, United Network for Organ Sharing

Box 29.1. Metabolic Liver Diseases

Inborn errors of carbohydrate metabolism
- Glycogen storage disease

Inborn errors of protein metabolism
- Tyrosinemia
- Urea cycle defects

Inborn errors of lipid metabolism
- Gaucher disease
- Niemann-Pick disease

Inborn errors of bile acid metabolism
- Byler disease
- Benign recurrent cholestasis

Inborn errors of copper metabolism
- Wilson disease

Inborn errors of iron metabolism
- Hereditary hemochromatosis
- Non-*HFE* hereditary iron overload disorders

Unclassified
- $Alpha_1$-antitrypsin deficiency
- Cystic fibrosis

Adapted from Ghishan FK. Inborn errors of metabolism that lead to permanent hepatic injury. In: Boyer TD, Manns MP, Sanyal AJ, editors. Zakim and Boyer's Hepatology: a textbook of liver disease. 6th ed. Philadelphia (PA): Saunders; c2013. p. 1155-201. Used with permission.

Clinical Features

The classic presentation of A1ATD is premature emphysema (especially in nonsmokers) and liver disease. This deficiency is also an important cause of childhood liver disease, often presenting as a neonatal hepatitis. The clinical manifestations of the deficiency are affected by the phenotype as well as by environmental factors, such as tobacco exposure and alcohol use.

In the only population-based study performed, the Swedish neonatal screening study identified 127 children deficient for A1AT who were followed prospectively through age 18 years. Neonatal cholestasis developed in 11%, and 6% had other liver disease without jaundice. Liver test results were abnormal 1 to 2 months after birth and usually normalized by 6 months. A small proportion of children either had end-stage liver disease or presented with acute liver failure in infancy. Most of the children (83%) were healthy throughout childhood, although most had abnormal liver test results in early life.

In adolescents and adults, A1ATD may cause chronic hepatitis or cirrhosis. This deficiency should be considered as a cause of abnormal liver enzyme levels in patients for which other common causes of liver disease, such as viral hepatitis, have been excluded. For adults with the Pi*ZZ phenotype, it has been estimated that cirrhosis will develop in 2% of those between 20 and 50 years old and in 19% of those older than 50 years. Patients with the Pi*MZ phenotype, which produces an intermediate degree of deficiency, are at some risk for chronic liver disease. It is more likely, however, that the Pi*MZ phenotype is a cofactor for the development of liver disease, along with other forms of liver injury such as nonalcoholic fatty liver disease. Several studies have noted an increased prevalence of the Pi*MZ phenotype among those undergoing orthotopic liver transplant for cryptogenic cirrhosis compared with those having orthotopic liver transplant for other indications. Adults with cirrhosis due to A1ATD have a greatly increased risk of hepatocellular carcinoma, with some studies reporting a prevalence of primary liver cancer of up to 30%.

Diagnosis and Evaluation

The diagnosis of A1ATD is made by A1AT phenotyping or genotyping. Serum levels of A1AT are not useful for diagnosing the deficiency because they may be falsely increased (in inflammatory conditions, malignancy, or pregnancy or with estrogen supplementation) or spuriously decreased (by nephrotic syndrome or protein-losing enteropathy). Also, the serum levels of A1AT do not correlate with liver damage, although they do predict lung damage.

Liver disease due to A1ATD is confirmed by characteristic findings in liver biopsy samples. Biopsy is also useful in staging the degree of hepatic fibrosis. The characteristic finding is the presence of eosinophilic, periodic acid-Schiff–positive, diastase-resistant (ie, PAS-D positive) globules in the endoplasmic reticulum of periportal hepatocytes. Because these globules may be present also in heterozygotes and in homozygotes without liver disease, their presence alone does not imply liver disease. Furthermore, because the globules may be distributed variably throughout the liver, their absence does not exclude the diagnosis of A1ATD. The histologic features of the liver in A1ATD are shown in Figure 29.1.

Patients with cirrhosis due to A1ATD should be enrolled in a surveillance program for hepatocellular carcinoma (typically with ultrasonography every 6 months). Patients with diagnosed liver disease due to A1ATD should be evaluated also for the presence of coexisting lung disease, especially if they have phenotype Pi*ZZ or are smokers. Baseline pulmonary function testing and chest radiography are recommended.

Treatment

No effective medical therapy is available for liver disease due to A1ATD. Although A1AT infusions are available, their role is limited to patients with A1ATD-related lung disease (because infusions of A1AT do not improve the accumulation of abnormal A1AT protein globules within hepatocytes). The mainstay of therapy is avoidance of alcohol and other hepatotoxins and maintenance of a healthy weight. Furthermore, patients should be advised to refrain from smoking to decrease the risk of emphysema.

Once advanced liver disease develops, liver transplant is the only definitive therapy. A1ATD is the most common metabolic indication for liver transplant in adults. Liver transplant corrects the consequences of portal hypertension, and the recipient assumes the *Pi* phenotype of the donor. Long-term outcomes for A1ATD after liver transplant are excellent.

A1ATD may be amenable to somatic gene therapy. Gene therapy probably would be beneficial only for the lung disease unless a method of delivering the corrected gene product to the endoplasmic reticulum of hepatocytes were available. Gene therapy continues to be an area of research, but it is not routinely clinically available.

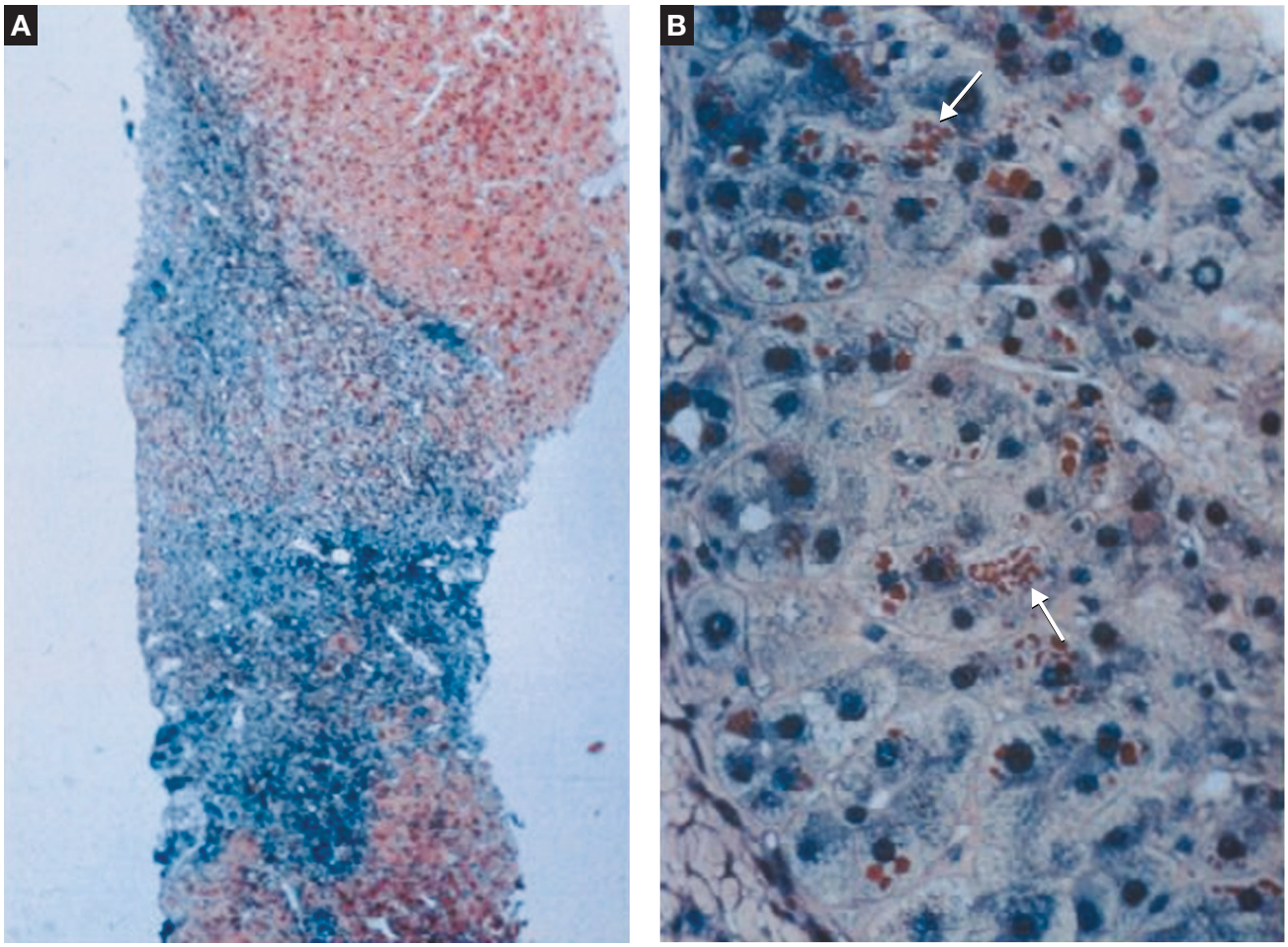

Figure 29.1. Histologic Features of the Liver in Alpha$_1$-Antitrypsin Deficiency. A, Low-power view. B, high-power view. Characteristic periodic acid-Schiff–positive, diastase-resistant globules (arrows) have accumulated in hepatocytes.

Wilson Disease

Wilson disease is an inherited disorder of intrahepatic copper metabolism characterized by the deposition of excess copper in the liver, brain, cornea, and other organs. It is a rare disorder that typically manifests in children, adolescents, and young adults. Patients with this disease may present with acute liver failure, chronic liver disease, hemolysis, or neuropsychiatric symptoms (or a combination of these).

Inheritance and Gene Function

Wilson disease is a somatic autosomal recessive disorder. The gene (*ATP7B*) associated with the disease is on chromosome 13 and codes for a copper-transporting P-type ATPase located predominantly in the endoplasmic reticulum and biliary canalicular membrane of hepatocytes. Although Wilson disease is a rare disorder, it is probably underdiagnosed. Approximately 1 per 30,000 persons are homozygous and 1 per 100 are heterozygous carriers of a Wilson disease gene mutation. To date, more than 100 mutations of *ATP7B* have been described. Attempts to correlate genotype with phenotype have not shown a consistent pattern and are not clinically useful. Approximately 30% to 40% of North American and European patients with Wilson disease have the H1069Q mutation.

Unlike hereditary hemochromatosis, in which approximately 90% of cases are homozygous for the C282Y mutation (see the Hereditary Hemochromatosis section below), the majority of patients with Wilson disease are compound heterozygotes (1 copy of 2 different mutations). The number of clinically important mutations makes genetic testing less useful for this disease than for hereditary hemochromatosis. Genetic testing is most valuable for screening the siblings of an affected proband in whom the specific mutations are known.

Copper Metabolism and Pathophysiology

Copper is an essential trace element that is necessary as a cofactor for many proteins. Dietary copper is absorbed in the proximal small bowel. Copper homeostasis is maintained through the biliary excretion of excess copper by active transport with a metal-transporting ATPase. Any disease that impairs biliary excretion (eg, chronic cholestatic biliary disorders such as primary biliary cirrhosis or primary sclerosing cholangitis) can cause increases in the level of hepatic copper. In Wilson disease, intestinal copper absorption is normal but biliary excretion of copper is decreased, leading to marked copper overload and ultimately end-organ toxicity.

Copper toxicity has a major role in the pathogenesis of the disease. Copper accumulates in the liver and eventually appears in other organs, particularly the brain and the eye (specifically, the cornea). Excess copper exerts its toxic effect by the generation of free radicals that result in lipid peroxidation, similar to

the mechanism proposed for iron-induced damage in hereditary hemochromatosis. Deficiency of ceruloplasmin is not the cause of Wilson disease; rather, it is an effect of the abnormal cellular trafficking of copper.

Clinical Features

Wilson disease has various clinical manifestations ranging from asymptomatic patients to those with crippling neurologic symptoms or acute liver failure. Wilson disease is a disease of young persons; the typical age at presentation is from 12 to 23 years. Hepatic manifestations tend to be more common in childhood, whereas neurologic symptoms tend to appear in the second and third decades of life. Although age alone should not be used to exclude Wilson disease, it is extremely rare to manifest initially in patients older than 40 years.

The 5 main categories of clinical presentation are hepatic, neurologic, psychiatric, hematologic, and ophthalmologic. In a large clinical series, the initial clinical manifestations were hepatic in 42% of patients, neurologic in 34%, psychiatric in 10%, and hematologic in 12%.

Hepatic Manifestations

Patients with Wilson disease can present with any form of liver disease, including asymptomatic abnormalities in liver test results, chronic hepatitis, and cirrhosis. Reports of hepatocellular cancer in Wilson disease are rare, even though many patients have advanced fibrosis at a young age. Although Wilson disease should be considered in all young patients with liver disease, it is responsible for less than 5% of cases of chronic hepatitis in persons younger than 35 years.

Acute liver failure is a catastrophic manifestation and may be the initial presentation of patients with Wilson disease. Acute liver failure due to this disease is 4 times more common in female patients than male patients. Fulminant Wilson disease should be suspected in any young patient with acute liver failure, especially if it is associated with hemolytic anemia. Patients with fulminant Wilson disease require urgent liver transplant because there is no other effective therapy. In the United States, patients with fulminant Wilson disease awaiting liver transplant are given a high priority for deceased donor organ allocation (United Network for Organ Sharing [UNOS] status 1).

Neuropsychiatric Manifestations

The typical neurologic manifestations of Wilson disease are dominated by extrapyramidal motor symptoms, including rigidity or spasticity, tremor, ataxia, dysarthria, drooling, and involuntary movements. Dementia and seizures are rare. Psychiatric problems may be dramatic, with psychosis or depression, or they may be subtle and manifested as behavioral problems or declining performance in school. Children are often classified as having behavioral problems or learning disabilities until progressive and sometimes irreversible neurologic symptoms begin to develop.

Hematologic Manifestations

Patients may present first with a Coombs-negative hemolytic anemia, frequently seen in association with acute, severe, or fulminant hepatitis. A young patient with severe liver dysfunction and hemolytic anemia should be presumed to have Wilson disease until proved otherwise.

Ocular Manifestations

Occasionally, Wilson disease is identified because of incidental eye findings, or the ocular manifestations may be noted during the evaluation of patients with suspected Wilson disease. Kayser-Fleischer rings represent copper deposition in the periphery of the cornea. These rings are frequently present in patients with neurologic manifestations of Wilson disease, but the absence of the rings does not exclude the disease. Prominent Kayser-Fleischer rings may be seen on direct examination, but more subtle rings may require slit-lamp examination. Sunflower cataracts are seen only with a slit lamp and do not interfere with vision. The ocular manifestations in Wilson disease are shown in Figure 29.2.

Other Manifestations

Wilson disease is associated also with proximal or distal renal tubular acidosis and nephrolithiasis. Another manifestation is azure lunulae, a blue discoloration of the base of the fingernails that is an uncommon but characteristic finding.

Diagnosis and Evaluation

The diagnosis of Wilson disease requires a strong clinical suspicion because of the multitude of potential manifestations. The

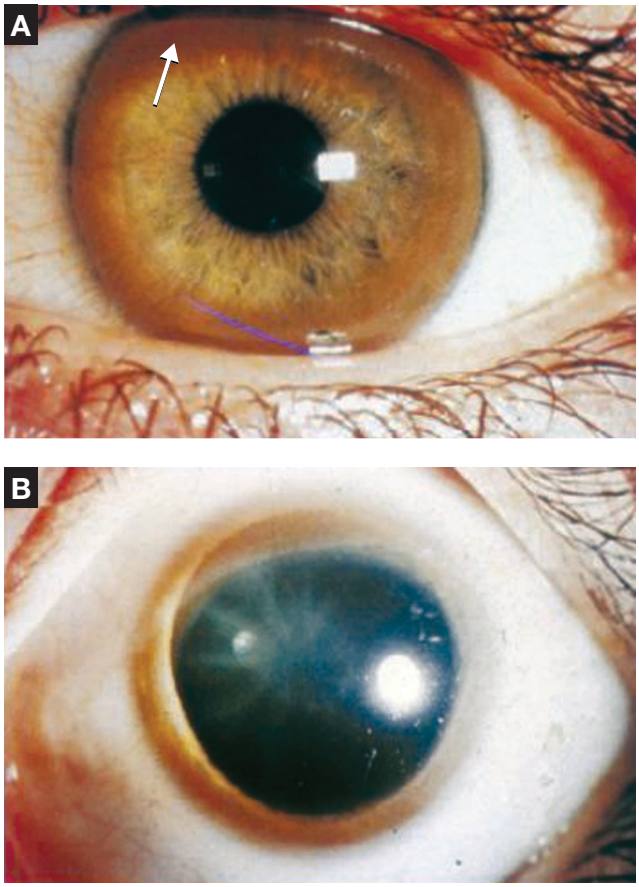

Figure 29.2. Ocular Manifestations in Wilson Disease. A, Kayser-Fleischer ring (arrow). B, Sunflower cataract. (Adapted from Zucker SD, Gollan JL. Wilson's disease and hepatic copper toxicosis. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. 3rd ed. Philadelphia [PA]: WB Saunders; c1996. p. 1405-39. Used with permission.)

disease should be considered in any person younger than 30 years who has liver disease. The combination of liver disease and extrapyramidal motor abnormalities should strongly suggest Wilson disease. The combination of severe liver disease and nonimmune hemolytic anemia should be considered Wilson disease until definitively proved otherwise.

Liver chemistry values are frequently abnormal in patients with Wilson disease, and characteristic patterns may serve as a clinical clue, but they are not consistent enough to be confirmatory. The alkaline phosphatase level is often low, and the serum aminotransferase levels tend to be increased less than would be expected from other signs of liver necrosis. Uric acid levels are usually low or undetectable, often because of concomitant proximal renal tubular acidosis. Serum copper levels are of limited usefulness because they may be low, normal, or increased—normal serum copper levels do not exclude Wilson disease.

The initial evaluation for suspected Wilson disease should include 1) determination of the serum ceruloplasmin level, 2) a 24-hour urine collection for copper quantification, and 3) a slit-lamp examination for Kayser-Fleischer rings. The serum level of ceruloplasmin is less than 20 mg/dL in 95% of patients with Wilson disease. Even though the level of ceruloplasmin can be increased nonspecifically as an acute phase reactant or as a result of estrogen administration, a level higher than 30 mg/dL essentially excludes the diagnosis of Wilson disease except in rare patients who present with fulminant hepatitis. Low ceruloplasmin levels must be interpreted with caution because any chronic liver disease with synthetic dysfunction or protein-losing states may be associated with a ceruloplasmin level that is lower than normal. Urinary copper excretion can be increased in other liver diseases; however, a value less than 100 μg daily in a patient with clinical disease would be very unusual in symptomatic Wilson disease. A low rate of urinary copper excretion may indicate acquired copper deficiency. This may be confusing because cases of severe copper deficiency may be associated with neurologic symptoms. The neurologic syndrome in these cases is myelopathy with weakness and ataxia.

In most cases, liver biopsy is necessary to confirm the diagnosis of Wilson disease, particularly in the absence of Kayser-Fleischer rings or characteristic neurologic symptoms. Liver morphologic features are nonspecific in Wilson disease. Often, steatosis is present, and glycogenated nuclei are common. The gold standard for confirming the diagnosis of the disease is quantitative tissue copper analysis. A normal liver concentration of copper (<35 μg/g dry weight) excludes the diagnosis. Most patients with the disease have liver copper concentrations greater than 250 μg/g dry weight, but this is not a specific finding and may occur in chronic cholestatic conditions or, rarely, in autoimmune hepatitis. Unlike hereditary hemochromatosis, children with Wilson disease may already have marked liver fibrosis; thus, in children, liver biopsy should be strongly considered to stage the liver disease.

Treatment

Treatment of Wilson disease is lifelong. Because many patients with Wilson disease are adolescents or young adults, adherence to therapy can be a problem, especially among asymptomatic patients. Therapies for Wilson disease can be divided broadly into 2 categories: chelating agents that remove copper from the body and agents that inhibit intestinal absorption of dietary copper. Liver transplant also is indicated as a treatment of fulminant Wilson disease (acute liver failure often associated with hemolysis) or for patients with complications of cirrhosis from the disease.

Chelating Agents

Patients with symptomatic or clinically evident disease should be treated initially with chelating agents. Penicillamine and trientine are metal chelators that induce the urinary excretion of copper. Both agents have been approved for the treatment of Wilson disease. Penicillamine is effective therapy and historically has been considered as first-line treatment, but it has numerous adverse effects. Up to 20% of patients experience drug toxicity, including hypersensitivity reactions, bone marrow suppression, proteinuria, autoimmune disorders, and dermatologic conditions. Importantly, as many as 20% of patients with neurologic symptoms may experience worsening of their symptoms during the first month of treatment. This deterioration is irreversible in some patients. Therefore, trientine should be considered as initial therapy for patients with neurologic symptoms from Wilson disease.

Trientine was introduced as an alternative to penicillamine. However, because of a lower incidence of adverse effects, trientine should be the first choice for treatment. It is given in doses similar to those for penicillamine and also has satisfactory long-term efficacy. The cupruresis is less pronounced than with penicillamine, but an initial increase is expected. Occasionally, iron deficiency may develop because of sideroblastic anemia. Tetrathiomolybdate has shown promise as an effective therapy; however, regulatory approval is still pending in the United States and Canada. Dosing of agents and monitoring for patients with Wilson disease are outlined in Table 29.1.

Treatment response to chelator therapy is demonstrated by an acute increase in urinary copper excretion that gradually plateaus at a lower level over 6 to 12 months. Initially, urinary copper output is often more than 2,000 μg daily, decreasing to 400 to 500 μg daily in the maintenance phase. The urinary and serum levels of copper and the ceruloplasmin level should be measured and a complete blood cell count should be performed weekly during the first month and then every 1 or 2 months during the first 6 months. Patients whose condition is stable can then be followed annually. The slit-lamp examination should be repeated annually to document the disappearance of Kayser-Fleischer rings (if present).

Inhibition of Copper Absorption

In the intestinal epithelium, zinc acetate induces the synthesis of metallothionein, which preferentially binds copper and prevents its absorption. Zinc therapy is indicated for presymptomatic patients and pregnant women. It also may be used as maintenance therapy for patients presenting with symptomatic disease following initial chelation therapy to remove excess copper (typically after 6-12 months). Treatment is monitored by checking urinary levels of zinc and copper. The urinary excretion of zinc should be at least 2,000 μg daily.

For pregnant women with Wilson disease, penicillamine is probably safe, but zinc is a better choice for patients whose condition is stable. The teratogenicity of trientine is unknown, and it should not be given during pregnancy.

Liver Transplant

The indications for liver transplant include acute liver failure, end-stage liver disease unresponsive to medical therapy, and

Table 29.1. Treatment of Wilson Disease

	Daily Dose by Mouth			
Agent	*Initial*	*Target*	*Monitoring*	*Comments*
Penicillamine	250-500 mg	1-2 g, divided into 2-4 doses	CBC, ceruloplasmin, and urinary and serum copper levels should be measured weekly during first month, then every 1 or 2 mo during first 6 mo; once stable, follow annually Slit-lamp examination to document disappearance of K-F rings, if present	Administer with pyridoxine because penicillamine can deplete vitamin B_6 Do not administer to patients with neurologic symptoms because will worsen symptoms in 20%
Trientine	250-500 mg	1-2 g, divided into 2-4 doses	CBC, ceruloplasmin, and urinary and serum copper levels should be measured weekly during first month, then every 1 or 2 mo during first 6 mo; once stable, follow annually Slit-lamp examination to document disappearance of K-F rings, if present	First-line therapy for most patients Dosing and monitoring as with penicillamine May cause sideroblastic anemia
Zinc acetate	50 mg, 3 times	50 mg, 3 times	Urinary copper and zinc excretion should be >2,000 µg daily	Initial therapy for presymptomatic patients and pregnant patients Can be used as maintenance therapy after copper depletion with trientine or penicillamine

Abbreviations: CBC, complete blood cell count; K-F, Kayser-Fleischer.

chronic deterioration of liver function despite long-term therapy. Medical therapy is not effective in reversing fulminant Wilson disease, and patients with fulminant disease require urgent liver transplant and are given high priority for donor organ allocation (UNOS status 1). Outcomes for liver transplant in patients with fulminant disease are good, with a 1-year survival rate of 73%. Among those with chronic liver failure, the 1-year survival rate is about 90%. There are anecdotal reports of marked neurologic improvement after liver transplant, but transplant performed solely for refractory neurologic symptoms is considered experimental because of the limited experience and uncertain outcome.

Family Screening

After Wilson disease has been diagnosed, family members should have screening tests for the disease. Testing should be directed at siblings because each has about a 25% chance of having the disease. If treatment is begun in the presymptomatic phase of the disease before cirrhosis is established, disease progression can be prevented. Because copper metabolism in infancy and early childhood may simulate Wilson disease, children should not be tested before 5 years of age. Screening should include aminotransferase and ceruloplasmin levels and a slit-lamp examination for Kayser-Fleischer rings. If the results are normal, screening should be repeated every 5 years until age 20. If the ceruloplasmin level is less than 20 mg/dL but there are no Kayser-Fleischer rings or convincing neurologic symptoms, liver biopsy may be necessary. Genetic testing generally is used for screening once the pattern in the index case is known. This may be of value if standard copper test results are equivocal.

Hereditary Hemochromatosis

Hereditary hemochromatosis is an inherited disorder of iron metabolism characterized by the deposition of excess iron in the liver, heart, joints, pancreas, skin, testes, and other organs. Patients with hereditary hemochromatosis may present with chronic liver disease, cardiomyopathy, or arthropathy.

Inheritance and Gene Function

Hereditary hemochromatosis is a somatic autosomal recessive disorder. The gene associated with this disorder is the *HFE* gene, on the short arm of chromosome 6. In contrast to the large number of mutations of the *ATP7B* gene for Wilson disease, the *HFE* gene has 2 common point mutations, C282Y and H63D. Other mutations have been described, but they probably are not of major clinical importance. About 90% of patients with iron overload consistent with hereditary hemochromatosis are homozygous for the C282Y mutation. The *HFE* gene is involved in regulating dietary iron absorption. The HFE protein binds to the transferrin receptor and functions to signal when body iron stores are adequate. Mutant *HFE* fails to downregulate iron absorption from enterocytes despite adequate iron levels, leading to iron overload.

Unlike Wilson disease, hereditary hemochromatosis is not a rare disorder. It is the most common single-gene, inherited disorder in the US white population. Approximately 1 in every 200 to 300 white persons in the United States is homozygous for the hemochromatosis mutation, and at least 1 in every 10 is a heterozygous carrier.

Iron Metabolism and Pathophysiology

Iron metabolism is relatively complex. The pathophysiology of hereditary hemochromatosis can be summarized as the failure to downregulate dietary iron absorption in the presence of adequate or excess body iron stores. However, not all iron overload is due to hereditary hemochromatosis; excess iron administration, multiple blood transfusions, or hematopoietic disorders can result in secondary iron overload states.

Dietary iron absorbed by enterocytes is transported through the basolateral membrane into the bloodstream by the transmembrane transporter ferroportin. *HFE* and transferrin receptor 1 are involved in signaling adequate iron stores. This, in turn, leads to increased expression of the hepcidin protein, which inhibits iron release from ferroportin into the bloodstream. In the presence of mutant *HFE*, hepcidin is not upregulated, leading enterocytes to detect a state of iron deficiency and continue to avidly transport

dietary iron into the bloodstream. This uninhibited iron absorption leads to iron excess and eventually end-organ toxicity.

Clinical Features

Because persons with hereditary hemochromatosis absorb only a few more milligrams of iron each day than needed, clinical manifestations generally occur after the fifth decade of life, when 15 to 40 g of iron have accumulated (normal body iron stores are approximately 4 g). Among C282Y homozygotes, approximately 30% of men and 2% to 10% of women have biochemical or clinical evidence of iron overload. The lower frequency of clinical iron overload among women than men is likely due to menstrual and pregnancy-related blood loss. Additional factors that influence disease expression include age, dietary iron intake, and unknown factors, including mutations in genes other than *HFE*. Liver disease is also affected by alcohol consumption and comorbid liver disease (eg, hepatitis C), which accelerate hepatic fibrosis.

In the past, hereditary hemochromatosis usually was diagnosed at an advanced stage. The classic description of hereditary hemochromatosis, bronze diabetes, resulted from cutaneous hyperpigmentation, diabetes mellitus, and cirrhosis. Currently, the disease is diagnosed in most patients at an asymptomatic stage through laboratory studies. Clinical manifestations of the disease include fatigue, hepatomegaly, abnormal liver enzyme levels, cirrhosis, hepatocellular carcinoma, cardiomyopathy, cardiac conduction disorders, hypothyroidism, hypogonadism, erectile dysfunction, and arthropathy. An example of hemochromatosis arthropathy is shown in Figure 29.3. Most, if not all, clinical manifestations are preventable if the disease is diagnosed early and treated appropriately. Hepatomegaly, abnormal liver test results, skin bronzing, cardiomyopathy, and cardiac conduction disorders may reverse after iron depletion, although most other clinical manifestations are not reversible.

The development of hepatocellular carcinoma is a major consequence of hereditary hemochromatosis. In up to one-third of patients with hereditary hemochromatosis and cirrhosis, hepatocellular carcinoma develops and often is the cause of death. The presence of hemochromatosis imparts a 200-fold increased risk of liver cancer, with most cases involving patients with cirrhosis. The increased risk of hepatocellular carcinoma does not improve after iron depletion. Patients with hereditary hemochromatosis-related cirrhosis should have abdominal ultrasonography every 6 months to screen for hepatocellular carcinoma.

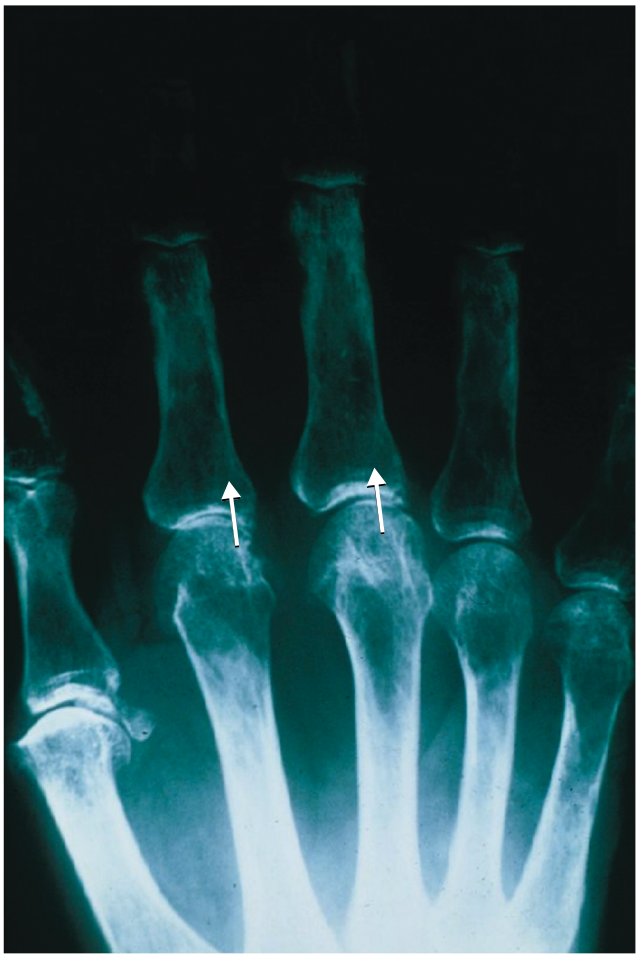

Figure 29.3. Hemochromatosis Arthropathy. A radiograph of the hand shows cartilage loss, marginal sclerosis, and osteophyte formation in the second and third metacarpophalangeal joints (arrows) without involvement of the fourth and fifth joints. Involvement of the second and third metacarpophalangeal joints is characteristic of hemochromatosis arthropathy. Occasionally, calcium pyrophosphate dihydrate crystals are present (chondrocalcinosis). (Adapted from Riely CA, Vera SR, Burrell MI, Koff RS. AGA Gastroenterology teaching project, unit 8: inherited liver disease. Used with permission.)

Diagnosis and Evaluation

Hereditary hemochromatosis is diagnosed on the basis of a combination of clinical, laboratory, and pathology criteria. Iron studies should show increased serum transferrin saturation (100 × [serum iron concentration/total iron-binding capacity]) and an increased serum ferritin level. The serum iron values show diurnal variation, and measurements may be affected by the ingestion of food. For this reason, serum iron levels should be measured early in the morning with the patient fasting. An increase in transferrin saturation is the earliest laboratory abnormality in hereditary hemochromatosis.

The serum concentration of ferritin is usually a reasonable estimate of total body iron stores. However, because ferritin is also an acute phase reactant, it is increased in various infectious and inflammatory conditions without any iron overload. This is a common pitfall in the diagnosis of hereditary hemochromatosis. Ferritin may be increased in 30% to 50% of patients who have viral hepatitis, nonalcoholic fatty liver disease, or alcoholic liver disease. For these reasons, ferritin should not be used as the initial screening test to detect hereditary hemochromatosis. A diagnostic algorithm for hereditary hemochromatosis is provided in Figure 29.4.

HFE Gene Testing

The *HFE* gene test is most useful for surveillance of adult first-degree relatives of an identified proband. *HFE* gene testing has replaced the HLA typing previously used to screen for hereditary hemochromatosis in relatives of affected persons. *HFE* gene testing is also often useful in cases of diagnostic uncertainty, such as iron overload associated with hepatitis C, alcoholic liver disease, or other causes of end-stage liver disease. Before the *HFE* gene test is performed, the person should be counseled about the risks, benefits, and alternatives of genetic testing, including the possibility of insurance or employment discrimination.

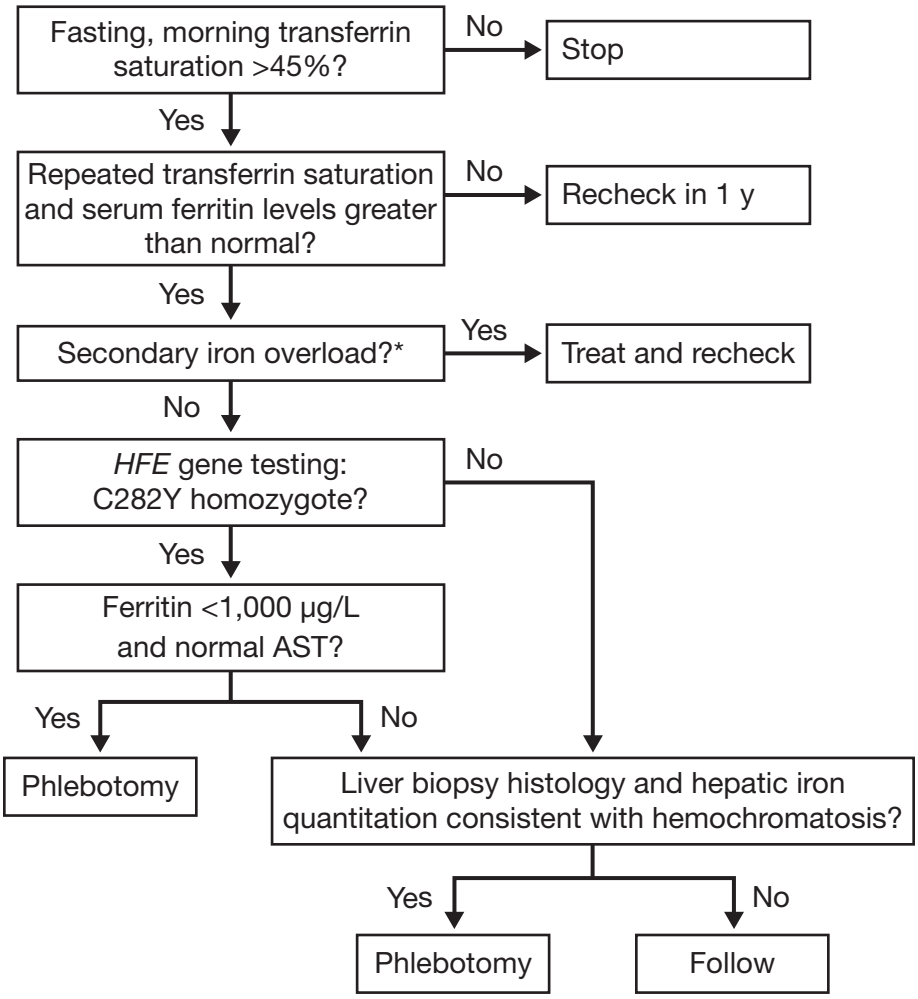

Figure 29.4. Diagnostic Algorithm for Hereditary Hemochromatosis. Asterisk indicates anemias with ineffective erythropoiesis, multiple blood transfusions, or oral or parenteral iron supplementation. AST indicates aspartate aminotransferase. (Adapted from Brandhagen DJ, Fairbanks VF, Batts KP, Thibodeau SN. Update on hereditary hemochromatosis and the *HFE* gene. Mayo Clin Proc. 1999 Sep;74[9]:917-21. Used with permission of Mayo Foundation for Medical Education and Research.)

Thus, *HFE* gene testing usually is not recommended for anyone younger than 18 years.

The 2 most common *HFE* mutations are C282Y and H63D. Together, they account for approximately 85% of cases of hereditary hemochromatosis. C282Y homozygotes are the most likely to present with clinically evident iron overload. Compound heterozygotes (C282Y/H63D) and H63D homozygotes have significantly lower rates of clinically evident iron overload (approximately 20%). Heterozygotes (single copy of C282Y or H63D) typically do not have iron overload; however, some have been observed to have slightly high (or high-normal) values on serum iron tests.

Liver Biopsy

Liver biopsy had an important role in the diagnosis of hereditary hemochromatosis before the *HFE* gene test was routinely available. Currently, however, liver biopsy is used only to assess cases with diagnostic uncertainty and to assess for the presence of advanced fibrosis or cirrhosis. In patients with iron overload who are C282Y homozygotes, liver biopsy is not necessary to confirm the diagnosis. Qualitative assessments of hepatic iron may be made with an iron stain (eg, Perls Prussian blue). In hereditary hemochromatosis, iron accumulates initially in periportal hepatocytes and eventually is distributed throughout the liver. This is in contrast to secondary iron overload in which iron often occurs predominantly in Kupffer cells. In severe iron overload, this distinction cannot be made reliably. The histologic features of the liver in hereditary hemochromatosis and secondary iron overload are shown in Figure 29.5.

The gold standard for diagnosis of hereditary hemochromatosis is the quantitative measurement of iron stores in the liver. Liver iron stores increase progressively with age, and this has led to the development of the hepatic iron index: the hepatic iron concentration in micromoles per gram dry weight of liver divided by the patient's age in years. A hepatic iron index greater than 1.9 is strongly suggestive of hereditary hemochromatosis.

Identifying patients who have hereditary hemochromatosis–related cirrhosis is critical because of the need to screen for complications of cirrhosis, including esophageal varices and the increased risk of hepatocellular cancer. Patients with hereditary hemochromatosis whose risk of having cirrhosis is minimal can be predicted by age and ferritin levels. In C282Y homozygotes younger than 40 years who have serum ferritin levels less than 1,000 µg/L and normal aspartate aminotransferase values, cirrhosis is unlikely and liver biopsy would be unnecessary.

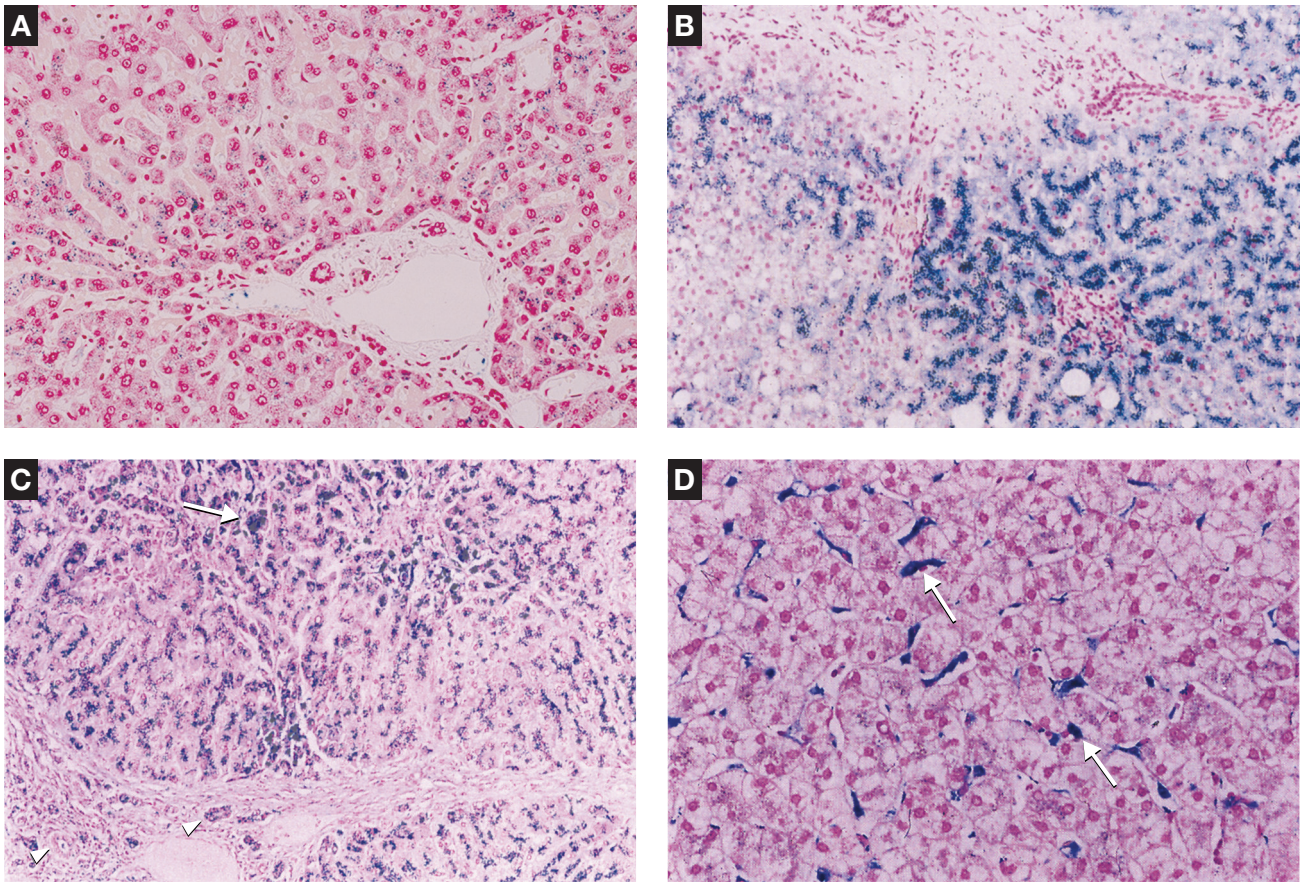

Figure 29.5. Iron Deposition in the Liver. A, Mild (grade 1 of 4) iron deposition in hepatocytes. B, Moderate hemosiderin deposition in precirrhotic homozygous hemochromatosis. Zone 1 hepatocytes are predominantly involved, biliary hemosiderin is not evident, and fibrosis has not yet occurred—all indicating relatively early precirrhotic disease (liver iron concentration, 10,307 µg/g dry weight; iron index, 3.2) (original magnification ×133). C, Marked hemosiderosis and cirrhosis in homozygous hemochromatosis. Although most iron is in hepatocytes, some Kupffer cells (arrow) and biliary iron (arrowheads) are also present (original magnification ×133). D, Kupffer cell hemosiderosis. The presence of hemosiderin in Kupffer cells alone (arrows) is typical of mild transfusion hemosiderosis, is nonspecific, and should not prompt further consideration of hemochromatosis (original magnification ×240). (A-D, Perls Prussian blue stain.) (A, adapted from Brandhagen DJ. Liver transplantation for hereditary hemochromatosis. Liver Transpl. 2001;7[8]:663-72, and B-D, adapted from Baldus WP, Batts KP, Brandhagen DJ. Liver biopsy in hemochromatosis. In: Barton JC, Edwards CQ, editors. Hemochromatosis: genetics, pathophysiology, diagnosis, and treatment. Cambridge: Cambridge University Press; c2000. p. 187-99. Used with permission.)

Consequently, liver biopsy is advisable for patients older than 40 years who have abnormal levels of aminotransferases or a ferritin concentration greater than 1,000 µg/L (or both) to definitively assess for the presence of cirrhosis.

Secondary Iron Overload

Not all iron overload is due to hereditary hemochromatosis, which should be distinguished from iron overload caused by other conditions. Secondary iron overload should be suspected in patients with chronic anemias who have ineffective erythropoiesis or have had multiple blood transfusions. In rare instances, prolonged iron supplementation can produce abnormal iron test results and, even more rarely, tissue iron overload.

A commonly encountered cause of abnormal iron test results is acute or chronic liver disease. Acute liver disease may be accompanied by a high ferritin level, usually with a normal transferrin saturation. Chronic liver disease, particularly if advanced, may result in abnormalities in ferritin and iron saturation that can mimic hereditary hemochromatosis. However, severe iron overload from hereditary hemochromatosis may be indistinguishable from that due to secondary causes. Patients with alcohol-related steatohepatitis may present with markedly increased ferritin levels. If the diagnosis is in doubt, these patients can be observed because alcohol-related increases in ferritin will decrease remarkably over a short period (3 months) with abstinence from alcohol. Patients with nonalcoholic fatty liver disease often present with increased liver enzyme and ferritin levels. This is clinically relevant because it is a frequent cause for referral and confusion. Despite hereditary hemochromatosis being a common disease, most patients with abnormal iron test results (particularly isolated elevated ferritin levels) do not have the disease.

Treatment

Hemochromatosis is a simple and satisfying disease to treat, and treatment before the development of end-organ damage can prevent serious morbidity and death. Treatment is iron depletion by therapeutic phlebotomy. Therapeutic phlebotomy is the preferred treatment because it is simple, relatively inexpensive, and effective. Dietary modifications are not advised because iron depletion cannot be achieved with dietary changes alone. Patients

should be counseled to refrain from taking iron supplements, including multivitamins with iron, and high-dose vitamin C supplements. Although iron chelators such as the parenteral agent deferoxamine and oral agent deferasirox are often administered to patients with secondary iron overload (particularly those with hematologic disorders who may not tolerate phlebotomy), they are associated with more adverse effects and are much less effective than phlebotomy.

Usually, the treatment of hereditary hemochromatosis is reserved for patients who have evidence of iron overload as indicated by an increase in the serum concentration of ferritin. Patients with *HFE* gene mutations without iron overload do not need phlebotomy (but should be monitored periodically). Therapeutic phlebotomy is divided into 2 phases: 1) During the initial phase, phlebotomy is performed frequently to deplete excess iron stores. 2) This is followed by lifelong maintenance phlebotomy to prevent the reaccumulation of excess iron.

The initial phase of phlebotomy begins with removal of 500 mL of blood weekly. The hemoglobin concentration should be measured just before each phlebotomy. Weekly phlebotomy should continue as long as the hemoglobin concentration is higher than a preselected value (usually 12-13 g/dL). If the concentration is less than the preselected value, phlebotomy should not be performed. Once the hemoglobin concentration remains below the preselected value for 3 consecutive weeks without phlebotomy, the serum concentration of ferritin and transferrin saturation should be determined again. Iron depletion is confirmed if the ferritin level is not more than 50 µg/L, with a low-normal transferrin saturation. When iron depletion has been achieved, most patients require maintenance phlebotomies about every 3 to 4 months to keep the ferritin level less than 50 µg/L. Once iron is depleted, patients should have iron stores checked every 1 to 2 years to adjust the frequency of maintenance phlebotomy as necessary.

Despite being common, hereditary hemochromatosis only rarely causes complications of cirrhosis and is an uncommon indication for orthotopic liver transplant, accounting for less than 1% of all liver transplants performed in the United States. Patients with hepatocellular carcinoma complicating hereditary hemochromatosis–related cirrhosis should be referred for consideration of liver transplant (the tumors must meet liver transplant criteria). The survival rate of patients with hereditary hemochromatosis undergoing liver transplant has improved in recent years and is now similar to that of liver transplant for other indications. The death of many liver transplant recipients who have hereditary hemochromatosis is caused by cardiac or infectious complications.

Family Screening

Currently, experts disagree about the usefulness of screening for hereditary hemochromatosis in the general population. Despite the disease fulfilling many of the criteria of a condition appropriate for population screening, some public health experts do not advocate screening. Screening for the disease in family members of affected individuals is crucial because 25% of siblings and 5% of children of a proband will have the disease. *HFE* gene testing should be considered also for siblings of C282Y heterozygotes. The spouse of an affected person may be tested to assess the risk to children. If the spouse does not have a mutation for *HFE*, the children will not be affected.

Non-*HFE* Hereditary Iron Overload Disorders

With the expanding understanding of the pathogenesis of hemochromatosis, several non-*HFE* forms of hereditary iron overload disorders have been identified. These should be considered when iron overload is documented in the absence of a secondary cause (eg, hemolysis) and *HFE* gene testing is negative. The clinical features are listed in Table 29.2.

Table 29.2. Non-*HFE* Hereditary Iron Overload Disorders

Disorder	*Laboratory Test Findings*	*Clinical Features*
TFR2 hemochromatosis	Elevated transferrin saturation	Younger at presentation than patients with *HFE* hemochromatosis (age 30-40 y)
	Elevated ferritin level	Hepatic, endocrine, and cardiovascular involvement
HAMP or *HJV* mutations	Elevated transferrin saturation	Severe iron overload phenotype
	Elevated ferritin level	Patients present at young age (15-20 y)
		Cardiomyopathy
Ferroportin disease	Low or normal transferrin saturation	Broad age range at presentation
	Elevated ferritin level	Splenic iron deposition
		Liver biopsy shows iron in Kupffer cells

Abbreviations: *HAMP*, hepcidin gene; *HJV*, hemojuvelin gene; *TFR2*, transferrin receptor 2 gene.

Table 29.3. Comparison of Hemochromatosis, Wilson Disease, and Alpha$_1$-Antitrypsin Deficiency

Feature	*Hemochromatosis*	*Wilson Disease*	*Alpha$_1$-Antitrypsin Deficiency*
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal codominant
Homozygote frequency	1:200 to 1:300	1:30,000	1:2,000
Heterozygote frequency	1:10	1:100	1:30
Gene	*HFE*	*ATP7B*	. . .
Number of mutations[a]	2 (C282Y, H63D)	>100	. . .
Chromosome	6	13	14
Diagnosis	Transferrin saturation, ferritin level, liver iron concentration, *HFE* gene test	Ceruloplasmin, slit-lamp examination for Kayser-Fleischer rings, urinary and liver copper quantification	Alpha$_1$-antitrypsin phenotype
Treatment	Phlebotomy	Penicillamine, trientine, or zinc	None or orthotopic liver transplant

[a] Clinically significant.

Summary

The features of hemochromatosis, Wilson disease, and A1ATD are summarized and compared in Table 29.3.

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30

Cholestatic Liver Disease

JAYANT A. TALWALKAR, MD, MPH

Cholestatic liver disease in adults without biliary obstruction encompasses a broad differential diagnosis. Drug-induced cholestasis may be the most common explanation for cholestasis in these patients. Primary biliary cirrhosis is the most common cholestatic liver disease in adults, and primary sclerosing cholangitis is about half as common as primary biliary cirrhosis. Other cholestatic conditions in adults include antimitochondrial antibody (AMA)-negative primary biliary cirrhosis, human immunodeficiency virus (HIV)-related cholangiopathy, and miscellaneous conditions.

Differential Diagnosis

The differential diagnosis for cholestasis in adults without biliary obstruction is listed in Box 30.1.

Primary Biliary Cirrhosis

Primary biliary cirrhosis has a prevalence of about 150 to 300 per million persons, involves women in 90% of cases, and is characterized by a positive serum AMA test in 95% of patients. These patients present with biochemical features of cholestasis and may be asymptomatic. Fatigue is the most common symptom, but it is nonspecific and not useful in establishing the diagnosis. Pruritus is less common but may occur in 30% of patients. Laboratory tests show elevations in serum alkaline phosphatase levels, while aminotransferase levels are usually elevated up to 5 times the upper limit of the reference range. Total bilirubin levels are often normal at diagnosis, while serum levels of cholesterol and IgM can be abnormally high. The most characteristic finding is a positive serum AMA test, which recognizes the lipoic acid binding site on an enzyme in the pyruvate dehydrogenase complex. The diagnosis often is established with the finding of a high titer of AMA in the appropriate clinical setting. Although liver biopsy helps confirm the diagnosis and provides information about histologic staging, it may not be required for diagnosis in most cases. Cross-sectional imaging studies such as ultrasonography, computed tomography, or magnetic resonance imaging can help exclude biliary obstruction. Direct cholangiography is not needed to establish this diagnosis.

AMA-Negative Primary Biliary Cirrhosis

AMA-negative primary biliary cirrhosis is characterized by clinical and histologic features identical to those of AMA-positive primary biliary cirrhosis. However, instead of having a positive AMA test, 95% of patients have either antinuclear or anti–smooth muscle antibodies. Occasionally, these patients are confused with those who have autoimmune hepatitis–primary biliary cirrhosis overlap syndrome, but the histologic features and biochemical profile generally help differentiate AMA-negative primary biliary cirrhosis from this syndrome.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is the next most common cholestatic condition in adults. About 70% of patients have inflammatory bowel disease, and, unlike primary biliary cirrhosis, primary sclerosing cholangitis is more common in men than in women. The age at onset is around 40 years, although the condition is diagnosed increasingly more often in younger patients. Positive serum AMA tests rarely are present (≤2% of patients), and there

Abbreviations: AMA, antimitochondrial antibody; ERCP, endoscopic retrograde cholangiopancreatography; HIV, human immunodeficiency virus

Box 30.1. Differential Diagnosis for Cholestasis in Adults Without Large Duct Biliary Obstruction

Drug-induced cholestasis
Primary biliary cirrhosis
AMA-negative primary biliary cirrhosis
Primary sclerosing cholangitis
Small duct primary sclerosing cholangitis
HIV-related cholangiopathy
Idiopathic adulthood ductopenia
Idiopathic biliary ductopenia
Cholestasis of pregnancy
Cystic fibrosis
Sarcoidosis
Granulomatous hepatitis

Abbreviations: AMA, antimitochondrial antibody; HIV, human immunodeficiency virus.

is no hallmark serologic test for primary sclerosing cholangitis. Unlike the diagnosis of primary biliary cirrhosis, the diagnosis of primary sclerosing cholangitis requires direct cholangiography. Occasionally, patients have normal cholangiographic findings, but the histologic and clinical features (ie, a history of inflammatory bowel disease) suggest primary sclerosing cholangitis. These patients are considered to have small duct primary sclerosing cholangitis, but a liver biopsy is needed to confirm that diagnosis. Biopsy specimens may show more fibrosis surrounding the bile ducts and less inflammation than seen in primary biliary cirrhosis, although these characteristic findings generally are not apparent.

HIV-Related Cholangiopathy

HIV-related cholangiopathy is defined as biliary obstruction due to infections that lead to biliary strictures. This was more common in HIV-infected patients before highly active antiretroviral therapy was introduced. Now the frequency is less. The usual organisms include *Cryptosporidium parvum*, microsporidia, cytomegalovirus, and *Cyclospora*. The infection due to these organisms typically involves the intrahepatic biliary system.

The condition usually occurs in patients with very low CD4 cell counts and may manifest with right upper quadrant pain and diarrhea; fever and jaundice are less common. Alkaline phosphatase levels usually are increased. Transaminase levels usually are elevated mildly, and jaundice is unusual and generally mild. Diagnosis is often made with endoscopic retrograde cholangiopancreatography (ERCP), with ultrasonography as the initial study. The cholangiographic patterns seen in more than half the patients are those of papillary stenosis and sclerosing cholangitis. Less common are patterns of intrahepatic and extrahepatic involvement without papillary stenosis, papillary stenosis alone, and intrahepatic involvement alone.

Often, treatment against the causative agent is ineffective. Treatment with highly active antiretroviral therapy decreases the percentage of patients with HIV infection that progresses to AIDS and may eventually prevent the development of biliary complications. If patients have obstruction, endoscopic therapy with dilation should be considered.

Treatment of Specific Conditions

Primary Biliary Cirrhosis

Currently, the accepted standard of care is ursodeoxycholic acid, 13 to 15 mg/kg daily in divided doses, for patients with any stage of primary biliary cirrhosis who have abnormal liver test findings. Patients who meet minimal listing criteria for liver transplant should be referred for evaluation, but there is no harm in initiating ursodeoxycholic acid therapy while awaiting a donor organ. Ursodeoxycholic acid therapy should be increased gradually over 1 to 2 weeks to avoid precipitating pruritus, which can occur if the full dose is given initially. Evidence to date supports the contention that ursodeoxycholic acid improves survival free of transplant, decreases the risk of cirrhosis and varices, and lowers lipid levels. Recent observational cohort studies also confirm the survival benefit from ursodeoxycholic acid among patients with earlier stages of the disease. However, not all patients have a response to ursodeoxycholic acid therapy. Approximately 25% to 30% of patients have an incomplete response to ursodeoxycholic acid and remain at risk of disease progression. During therapy, serum alkaline phosphatase values are used to define the response. Once ursodeoxycholic acid therapy is begun, it appears to be a lifelong need, and patients should be instructed accordingly. Adverse effects are minimal.

AMA-Negative Primary Biliary Cirrhosis

Patients with AMA-negative primary biliary cirrhosis typically have a similar response to ursodeoxycholic acid therapy when compared with patients with AMA-positive primary biliary cirrhosis. For patients with overlap syndrome with primary biliary cirrhosis and autoimmune hepatitis, most clinicians begin treatment with ursodeoxycholic acid, corticosteroids, or azathioprine (or a combination of these drugs) since patients with this form of primary biliary cirrhosis appear to have a higher risk of disease progression than patients with typical primary biliary cirrhosis.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is the most troublesome of the more common adult cholestatic liver diseases because no effective therapy is available. For treatment of primary sclerosing cholangitis, ursodeoxycholic acid in standard doses of 13 to 15 mg/kg per day, moderate doses of 17 to 23 mg/kg per day, or high doses of 28 to 30 mg/kg per day has not been shown to be effective. Patients may have evidence of rapidly progressive jaundice, may suddenly become pruritic, or may have fever with right upper quadrant pain. When any of these occur, cholangiography (usually ERCP) should be considered, although magnetic resonance cholangiography is also an alternative (Figure 30.1). Cholangiocarcinoma, choledocholithiasis, or a dominant stricture all can be responsible for these manifestations and can be differentiated best with ERCP. The endoscopic approach allows biopsy with brushing for suspected malignancy, extrication of biliary stones, or dilation of dominant strictures. The role of stenting after dilation has not been defined clearly but is typically performed when balloon dilation alone does not achieve adequate decompression.

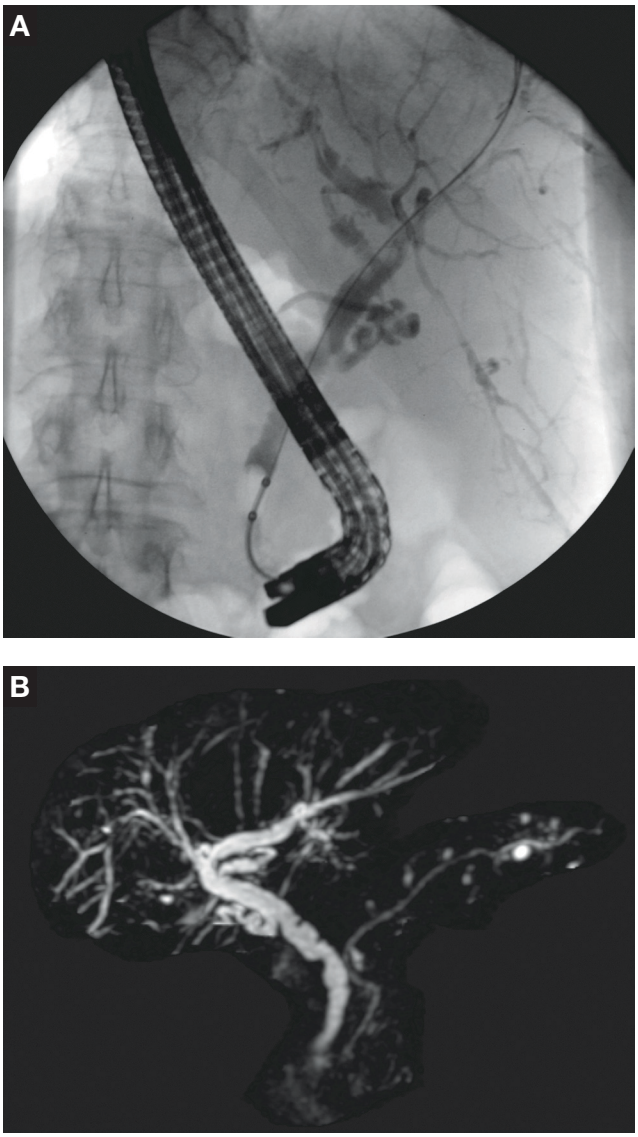

Figure 30.1. Diagnostic Imaging in Primary Sclerosing Cholangitis. Comparison of findings in the same patient with primary sclerosing cholangitis. A, Endoscopic retrograde cholangiopancreatography. B, Magnetic resonance cholangiography.

Management of Complications of Cholestasis

Vitamin Deficiency

Malabsorption and deficiency of fat-soluble vitamins may occur with cholestasis, especially if cholestasis is severe and cirrhosis develops. Serum levels of vitamins A, E, and D can be measured directly, and the serum level of vitamin K can be inferred from the prothrombin time. Replacement with water-soluble forms of the vitamins can be offered (vitamin A, 50,000 units twice weekly; vitamin E, 200 units twice daily; vitamin D, 50,000 units twice weekly; and vitamin K, 5 mg daily). Adequacy of replacement can be reassessed by measuring levels after 6 to 12 months of therapy.

Hypercholesterolemia

Hypercholesterolemia, common in patients with cholestasis, does not appear to be clearly associated with atherosclerosis. However, patients with risk factors for coronary heart disease may safely begin pharmacologic therapies (eg, statins) to improve lipid profiles.

Pruritus

Pruritus can be one of the most troublesome symptoms of patients with cholestasis. The severity of pruritus does not correlate closely with the severity of the underlying liver disease, and pruritus may resolve as the disease progresses. Ursodeoxycholic acid reduces pruritus in some patients with primary biliary cirrhosis, but for those who remain symptomatic, antihistamines (ie, diphenhydramine 25-50 mg by mouth at bedtime) may relieve the pruritus and permit sleep. Cholestyramine (one 4-g packet 3 or 4 times daily) may help relieve itching, but it can be unpleasant to use. Rifampin (150-300 mg twice daily) has a rapid onset of action and may be useful long term, although liver toxicity may develop in 15% of patients. Sertraline (75-100 mg daily) has also been shown to improve symptoms of pruritus. Naltrexone (50 mg daily) may be useful for some patients, although there is less experience with this drug than with the others. Liver transplant is available for patients who have severe, intolerable pruritus.

Bone Disease

Although the insufficient delivery of bile acids to the gut lumen in advanced cholestasis may lead to fat-soluble vitamin deficiency, osteomalacia due to vitamin D deficiency occurs in less than 5% of patients with osteopenic bone disease and cholestasis. Almost all bone disease evaluated in North American patients with cholestasis is due to osteoporosis, which is the result of insufficient bone matrix rather than a mineralization defect as found in osteomalacia. The cause of the osteoporosis is uncertain. These patients lose bone at a rate of about twice that of the normal population. About 33% of patients with primary biliary cirrhosis and about 20% of those with primary sclerosing cholangitis are osteopenic at the time of diagnosis, and about 10% of them experience vertebral fractures within a few years after diagnosis. Management of the bone disease includes exercise and adequate calcium intake with 1.5 g of elemental calcium daily in combination with vitamin D supplementation, if deficient. Postmenopausal women may have a response to hormone replacement therapy, usually given as patch therapy. Calcitonin therapy does not appear to be effective, but treatment with bisphosphonates has been shown to be effective.

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31

Drug-Induced Liver Injury[a]

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Despite increased awareness through the efforts of public and regulatory agencies, the syndrome known as *drug-induced liver injury* (DILI) is still a major public health problem in the United States and the world. Moreover, it is the single most common reason for US Food and Drug Administration (FDA) regulatory actions, including the removal of drugs from the marketplace. Although the frequency of this clinical syndrome is low within populations, DILI causes a significant clinical and economic burden. This chapter highlights new developments in the field of idiosyncratic DILI and provides information about DILI from acetaminophen.

Overview of Drug Metabolism

Orally administered drugs are lipid soluble, which allows them to be absorbed into cells and affect biologic processes. Drug-metabolizing systems convert the parent drug into water-soluble compounds, which are excreted into bile and urine. The metabolizing systems are divided into phase 1 and phase 2 reactions. Phase 1 reactions involve the cytochrome P450 (CYP) family of enzymes (the CYP3A subfamily is the most prominent) and include the addition of polar groups by oxidation, reduction, or hydrolysis. The metabolites formed by phase 1 reactions may be toxic if not subsequently excreted or further metabolized. Activity of phase 1 reactions is influenced by age, other drugs, and toxins (Box 31.1).

Phase 2 reactions further enhance the water solubility of a compound and generally involve conjugation of glucuronide, sulfate, acetate, glycine, or glutathione to a polar group. Occasionally, phase 2 reactions may affect the parent compound directly (ie, without a previous phase 1 reaction). Dietary factors, including nutritional status, can alter the activity of phase 2 reactions. The influence of alterations in drug-metabolizing systems on DILI is incompletely understood.

Clinical Epidemiology

Worldwide, the annual incidence rate of DILI is estimated to be between 13.9 and 24 cases per 100,000 persons, and the syndrome accounts for an estimated 3% to 9% of all adverse drug reactions reported to health authorities. The US Acute Liver Failure Study Group reported that acetaminophen and idiosyncratic drug reactions together account for approximately 50% of cases of acute liver failure in the United States. DILI is recognized as the most common identified cause of acute liver failure that requires liver transplant in the United States.

Epidemiologic data on DILI from prospective national registries have been published. The Regional Registry of Hepatotoxicity in Spain reported on 461 cases of DILI identified between 1994 and 2004. In this experience, hepatocellular damage was the most common pattern observed (58%), and nearly 12% of patients with jaundice at presentation died or required liver transplant, compared with only 4% of patients who were not jaundiced. The main causative medications were antibiotics (32% of cases), followed by central nervous system drugs (17% of cases), musculoskeletal drugs (17% of cases), and gastrointestinal drugs (10%

[a] The author thanks John J. Poterucha, MD, and Jayant A. Talwalkar, MD, who coauthored previous versions of this chapter.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP, cytochrome P450; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; DRESS, drug rash with eosinophilia and systemic symptoms; FDA, US Food and Drug Administration; HEV, hepatitis E virus; NHANES, National Health and Nutrition Examination Survey; NIH, National Institutes of Health; ULRR, upper limit of the reference range

Box 31.1. Drugs and Conditions That Affect Activity of the Cytochrome P450 (CYP) System

Inhibit CYP Activity

- Clarithromycin
- Erythromycin
- Fluconazole
- Older age
- Itraconazole
- Ketoconazole
- Ritonavir

Induce CYP Activity

- Carbamazepine
- Chronic alcohol use
- Phenobarbital
- Phenytoin
- Rifampin

of cases). Amoxicillin-clavulanic acid (Augmentin) was the most commonly implicated drug in this cohort.

Among the first 300 patients enrolled in the ongoing National Institutes of Health (NIH) Drug-Induced Liver Injury Network (DILIN) prospective study, an estimated 73% of cases resulted from taking a single prescription medication, 9% were attributed to herbal and dietary supplements, and 18% resulted from patients taking multiple agents. The mortality rate for patients followed for at least 6 months was 8%, although the cause of death was liver related in only 44% of patients. Among patients with DILI caused by a single prescription drug, the major classes of implicated agents were antimicrobials (46%), central nervous system agents (15%), immunomodulatory agents (5%), analgesics (5%), and lipid-lowering agents (3%). As in the Spanish registry, amoxicillin-clavulanic acid was the drug most commonly implicated.

In Iceland, cases of DILI were collected prospectively from 2010 through 2011. This study was unique in that it included an enumerated population (patients in Iceland) and was linked to a prescription database, allowing for improved estimation of incidence. Among the 96 cases identified, the crude annual incidence was 19.1 cases per 100,000 inhabitants (95% CI, 1.6-23.3 cases per 100,000 inhabitants). Again, amoxicillin-clavulanic acid was the most common drug, with an incidence of 1 in 729 users among inpatients and 1 in 2,350 among outpatients.

Mechanisms and Classification

DILI is largely an unsolved problem because of the limitations of our knowledge about the mechanisms of hepatic toxicity. Traditionally, the classification of injury patterns with DILI is based on specific histologic features such as inflammation, cholestasis, sinusoidal cell injury, immune-mediated damage, mitochondrial injury, and oxidative stress. Liver biopsy samples may show pathologic features such as prominent eosinophilia, granulomas, zonal or massive necrosis, or cholestasis with hepatitis. The usefulness of histologic examination of the liver is limited by knowledge about DILI, particularly information on the patterns of injury caused by various agents.

DILI can be divided broadly into direct chemical toxicity and idiosyncratic hepatotoxic reactions. *Direct chemical toxicity* is dose related; the most common example is the hepatotoxicity associated with acetaminophen. Direct toxicity usually occurs after a brief exposure. For a given drug, there is considerable variability in the dose required to cause toxicity, largely because of individual differences in drug metabolism. These differences can be genetic or due to exogenous effectors of drug metabolism.

In contrast to the relatively predictable dose-related toxicity from acetaminophen, the more common *idiosyncratic hepatotoxic reactions* appear related to genetic or environmental influences, or both, that are less well understood. Most drug-induced hepatotoxicity is metabolic, which involves the accumulation of toxic metabolites within hepatocytes, leading to necrosis and inflammation. Recent investigations have identified several categories of idiosyncratic DILI, as discussed below.

Hypersensitivity (Immunoallergic) Reaction

Liver injury from a hypersensitivity reaction usually follows 1 to 6 weeks of exposure to the drug and is accompanied by rash, fever, eosinophilia, and autoantibodies (alone or in combination) and recurs rapidly with rechallenge. Hypersensitivity features are seen in only about 20% of all cases of idiosyncratic DILI. DILI may also be seen in the context of stereotypical hypersensitivity reactions, such as drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Examples of drugs that can result in a hypersensitivity reaction are sulfonamides, amoxicillin-clavulanic acid, fluoroquinolones, phenytoin, and halothane.

Autoimmune Reaction

Autoimmune-mediated DILI may be caused by specific drugs, and the immune responses mimic those typically observed in de novo or idiopathic autoimmune hepatitis. Hydralazine, minocycline, and nitrofurantoin are drugs that are commonly associated with autoimmune DILI. Although it is difficult to distinguish autoimmune DILI from autoimmune hepatitis on the basis of history, laboratory findings, and histologic features, the absence of relapse after the withdrawal of corticosteroid therapy is highly suggestive of a drug-induced autoimmune reaction.

Cholestasis

Drug-induced cholestasis may occur as an acute disorder manifesting as canalicular (bland jaundice), hepatocanalicular (cholestatic hepatitis), or ductular (cholangiolar hepatitis) disease. Chronic cholestasis often results from the vanishing bile duct syndrome. Amoxicillin-clavulanic acid, erythromycin, trimethoprim-sulfamethoxazole, chlorpromazine, and oral contraceptives typically produce this form of DILI.

Steatosis

The deposition of small or large fat droplets in the liver is another recognized form of DILI. Microvesicular steatosis generally indicates acute disease, whereas macrovesicular steatosis or the combination of both microvesicular steatosis and macrovesicular

steatosis occurs with chronic exposure. Salicylate, valproate, amiodarone, and tamoxifen typically have been associated with this form of DILI.

Sinusoidal Obstruction Syndrome

Sinusoidal obstruction syndrome (formerly called venoocclusive disease) is diagnosed most often in patients who have received a myeloablative chemotherapeutic regimen before undergoing stem cell transplant for malignancy. This syndrome is seen also after exposure to 5-fluorouracil, oxaliplatin, cytosine arabinoside, actinomycin, dacarbazine, or plicamycin and, occasionally, azathioprine or 6-mercaptopurine. The diagnosis usually is based on the findings of hepatomegaly, weight gain, and hyperbilirubinemia. In some cases, histologic examination of the liver may be required. Management is largely supportive. The mortality rate is as high as 20%.

Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia is a rare disease that can lead to noncirrhotic portal hypertension with possible variceal hemorrhage but usually not ascites, hepatic encephalopathy, or synthetic dysfunction. While it can be seen with hematologic and rheumatologic conditions, it can also be found in association with several medications, including azathioprine, bleomycin, chlorambucil, cyclophosphamide, didanosine, and interleukin 2. The diagnosis should be made from liver histologic findings. Nodular regenerative hyperplasia is often overlooked since it is not easily appreciated with routine hematoxylin-eosin staining and requires a reticulin stain. The key histologic finding is small nodules around the portal tract with hypertrophied hepatocytes centrally and atrophic hepatocytes peripherally.

Peliosis Hepatis

Peliosis hepatis is a rare condition that manifests with multiple, dilated, blood-filled cavities in the liver and is associated with the following drugs: anabolic steroids, azathioprine, 6-mercaptopurine, danazol, tamoxifen, hydroxyurea, and oral contraceptives.

Risk Factors

Older age is associated with DILI caused by several common drugs, including isoniazid, erythromycin, amoxicillin-clavulanic acid, and nitrofurantoin. The reason that age affects the risk of DILI is not clear because phase 1 and phase 2 metabolizing enzyme activities are not altered markedly in older people. In contrast to earlier data, data from recent studies have not confirmed an increased predisposition to DILI among women in comparison with men. However, men and women might have differences in susceptibility to particular agents that cause DILI. For example, the majority of patients who have acute liver failure or require liver transplant because of DILI are women.

Recent studies also suggest that the daily dose of a drug might influence the development of DILI, which is in contrast to previous concepts. Among US prescription medicines, daily doses greater than 50 mg have been associated significantly with liver failure, liver transplant, and death from DILI. In the Swedish database, 9% of DILI cases were seen with oral medication doses of 10 mg or less daily, 14.2% of the patients were taking doses of 11 to 49 mg daily, and 77% were taking 50 mg or more daily. In the Spanish registry of 461 cases of DILI, 77% occurred in individuals taking 50 mg or more daily. Lipophilicity has recently been shown to be an important medication risk factor. Although not an independent risk factor, it has synergism with increased medication dose: high drug lipophilicity (logP ≥3) and high medication daily dose (>100 mg) increase the risk of DILI by as much as 14 times. Drugs with hepatic metabolism and hepatobiliary excretion are also associated with a higher risk of serious DILI. The role of alcohol in idiosyncratic DILI is debated, and the influence of underlying chronic liver disease as a risk factor for DILI is not fully understood. Clearly, patients with underlying liver disease have a higher risk of adverse outcomes than those without liver disease

Clinical Presentation

The clinical presentation of patients with DILI varies with the severity of injury to the liver. Patients with mild DILI (eg, an increase in the level of aspartate aminotransferase [AST], alanine aminotransferase [ALT], or alkaline phosphatase [ALP] [or a combination of these] and normal levels of total bilirubin) are either asymptomatic or have nonspecific symptoms such as fatigue and nausea. Moderate to severe DILI is accompanied often by abdominal pain, jaundice, and pruritus. Rash, fever, facial edema, and lymphadenopathy, in combination with eosinophilia or atypical lymphocytosis, may be present with hypersensitivity-type reactions. Coagulopathy, renal dysfunction, and mental status changes, when present, are seen typically in cases of fulminant DILI.

Diagnosis

There is no specific test for DILI. The maxim that "almost any drug can do almost anything" is important to consider when evaluating patients who have abnormal liver test results. Although the time between the initiation of medication use and the onset of hepatotoxicity varies, most cases of DILI occur within a year after treatment is started with the drug. DILI should be suspected when liver injury occurs soon after the initiation of treatment with an agent (within 4 weeks) or after an increase in the dose of an agent that had been administered previously.

Generally, the exclusion of other causes of liver disease is required before the diagnosis of DILI is made. Screening is required for hepatitis A, B, and C infections; alcoholic or autoimmune hepatitis; biliary tract disorders; and hemodynamic derangement. Although infections are less common, testing to exclude cytomegalovirus and Epstein-Barr virus infections is helpful. The possibility of hepatitis E involvement in suspected DILI cases was recently evaluated. Hepatitis E virus (HEV) IgG serologies were positive in 16% (50 of 318) of patients in the NIH DILIN series, with 3% possessing positive HEV IgM, suggestive of acute HEV infection. Of the participants in a National Health and Nutrition Examination Survey (NHANES) study (N=18,695), 21% were HEV seropositive, suggesting that HEV should no longer be considered a disease found only in developing countries. If a patient is suspected of having DILI with a hepatocellular pattern, HEV serology should be checked. Also, biliary abnormalities, through obstruction or infection, can injure the liver, as in cholecystitis and cholangitis. If this is suspected, the biliary tree should be imaged, initially with ultrasonography and then with computed tomography or magnetic resonance imaging (Figure 31.1). Also, resolution of the injury after withdrawal of the drug ("dechallenge") is helpful in confirming the

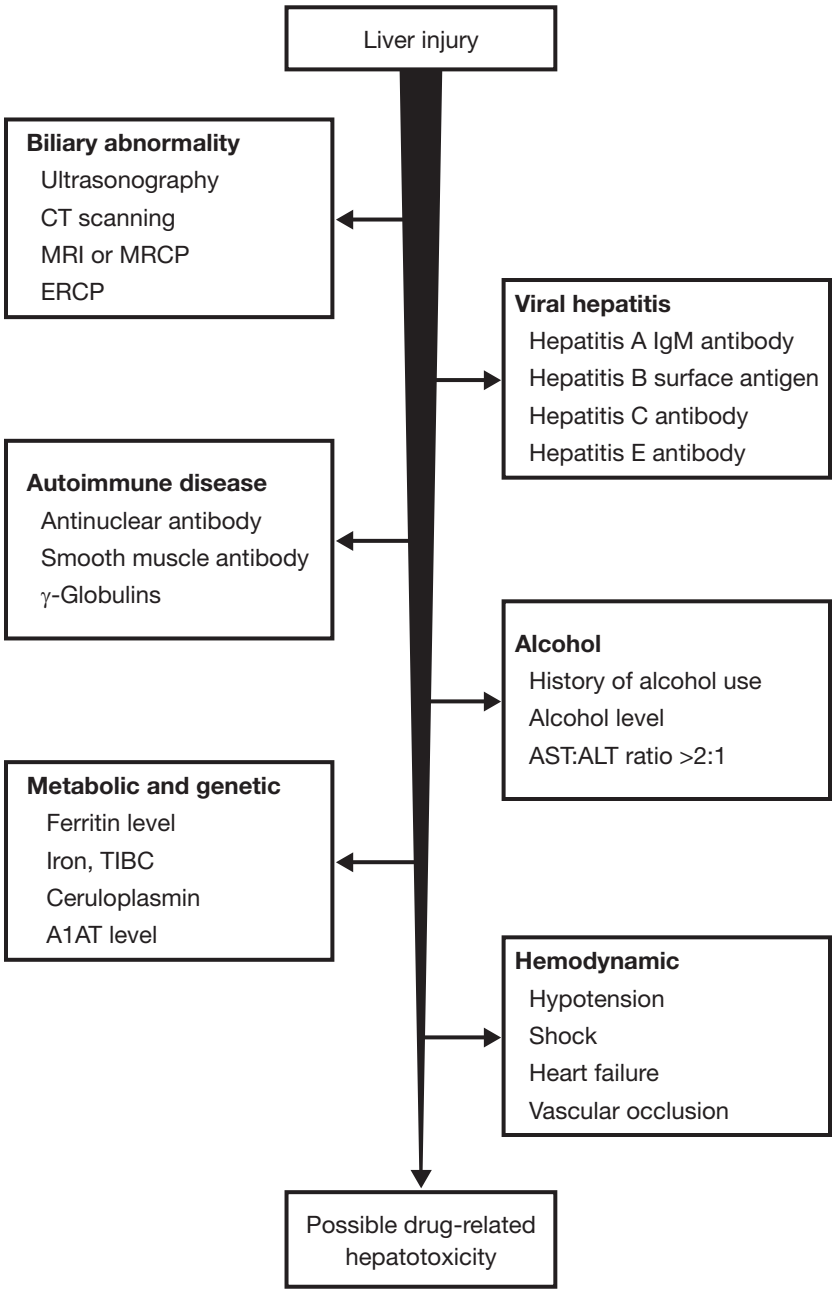

Figure 31.1. Diagnosis of Drug-Related Hepatotoxicity. There is no single test, including liver biopsy, that can be used to diagnose drug-related hepatotoxicity. Other causes of liver injury must first be considered with the use of a combination of serologic tests, imaging studies, and clues from the patient's history. A1AT indicates alpha$_1$-antitrypsin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; TIBC, total iron-binding capacity. (Adapted from Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006 Feb 16;354[7]:731-9. Used with permission.)

diagnosis of DILI, although the timing of improvement after the withdrawal varies.

DILI can be characterized biochemically as specific patterns of injury, such as hepatocellular, cholestatic, or mixed (Box 31.2), with the use of the *R* ratio, defined by the following equation:

$$R = \frac{\text{ALT (Reported as Multiple of ULRR)}}{\text{ALP (Reported as Multiple of ULRR)}},$$

where ULRR is upper limit of the reference range.

The liver injury pattern is hepatocellular when, at presentation, *R* exceeds 5, cholestatic when *R* is less than 2, and mixed when *R* is between 2 and 5. An important issue in calculating the *R* ratio is which values to use during the course of illness. For example, in the NIH DILIN study, *R* was calculated for 192 patients in whom DILI was thought to be due to a single agent. When *R* was calculated from the values obtained initially in the study, 57% of patients had the hepatocellular pattern of injury, 21% the mixed pattern, and 22% the cholestatic pattern. However, when *R* was calculated from the values at the time of the peak serum levels of bilirubin, 45% of patients had the hepatocellular pattern, 37%

Box 31.2. Patterns of Liver Injury With Certain Drugs

Hepatocellular (elevated ALT)

- Acarbose
- Acetaminophen
- Allopurinol
- Amiodarone
- Baclofen
- Bupropion
- Fluoxetine
- HAART drugs
- Isoniazid
- Ketoconazole
- Lisinopril
- Losartan
- Methotrexate
- NSAIDs
- Omeprazole
- Paraxetine
- Pyrazinamide
- Rifampin
- Risperidone
- Sertraline
- Statins
- Tetracyclines
- Trazodone
- Trovafloxacin
- Valproic acid

Mixed (elevated ALP and elevated ALT)

- Amitriptyline
- Azathioprine
- Captopril
- Carbamazepine
- Clindamycin
- Cyproheptadine
- Enalapril
- Flutamide
- Nitrofurantoin
- Phenobarbital
- Phenytoin
- Sulfonamides
- Trazodone
- Trimethoprim-sulfamethoxazole
- Verapamil

Cholestatic (elevated ALP)

- Amoxicillin-clavulanic acid
- Anabolic steroids
- Chlorpromazine
- Clopidogrel
- Erythromycins
- Estrogens
- Irbesartan
- Mirtazapine
- Oral contraceptives
- Phenothiazines
- Terbinafine
- Tricyclic antidepressants

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; HAART, highly active antiretroviral therapy; NSAID, nonsteroidal antiinflammatory drug.

Adapted from Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006 Feb 16;354(7):731-9. Used with permission.

the cholestatic pattern, and 17% the mixed pattern. Consequently, during DILI, a shift occurs in the ALP levels in relation to the ALT levels, and the later in the course of disease that values are obtained for calculating *R*, the more likely the patient is to have a cholestatic pattern of injury.

Many drugs cause mild, often insignificant, and transient increases in liver enzyme levels within a few months. These usually represent an adaptive response to the drug and do not necessitate withdrawal of treatment with the agent. For example, isoniazid increases the ALT level more than 3 times the ULRR in 15% of patients, but the enzyme levels usually normalize despite continued treatment. Generally, there should be concern about clinically significant DILI when liver enzyme levels increase more than 5 times the ULRR or when symptoms or impaired liver function is noted.

Ultimately, the level of certainty for making a diagnosis of DILI is related to the clinical history, chronology of exposure and injury, exclusion of competing causes, and previous knowledge of DILI with a specific agent through clinical experience and published data. Several causality assessment systems have been developed to identify the likelihood of suspected DILI and an implicated agent in research settings. Recent studies have shown that the results from these assessment systems are not well reproduced among multiple users, thus limiting their usefulness in research and clinical settings. More precise algorithms and ones that are easier to use in clinical practice are being developed.

Recent progress has been made related to biomarkers for DILI. MicroRNAs produced by the liver were evaluated in patients with acetaminophen liver injury or nonacetaminophen liver injury and in healthy controls. MicroRNA 122 was significantly elevated in patients with acetaminophen or nonacetaminophen liver injury compared with controls. Day 1 microRNA 122 levels correlated with the peak ALT level and were 2-fold higher in patients

meeting King's College criteria, but these relationships were not statistically significant. The clinical utility of microRNA requires further study. Protein adducts have also been investigated, and acetaminophen-cysteine adducts were found in 18% of 110 patients with indeterminate cases in the US Acute Liver Failure Study Group series as compared with 95% of the 199 patients with established acetaminophen-related acute liver failure. A recent proteomic analysis suggested that apolipoprotein E may be helpful in the diagnosis of DILI, but that will require further study.

Histologic Patterns

No unique histologic patterns unequivocally confirm the diagnosis of DILI. Notably, the results of histologic examination of the liver may vary with the timing of biopsy because hepatocellular injury is more prominent in the initial few weeks of injury; cholestatic features, however, are more prominent later in the course of disease. The 2 main categories of histologic change that can be observed are 1) acute and chronic hepatitis and 2) acute and chronic cholestasis/mixed hepatocellular-cholestatic injury.

Acute and Chronic Hepatitis

The dominant feature in this pattern is expansion of the portal area by a mononuclear infiltrate in the presence of interface hepatitis. Also, involvement of bile ducts by inflammation or reactive changes may be seen. The parenchyma has scattered foci of inflammation and usually apoptotic hepatocytes. At the severe end of liver injury, lobular disarray, areas of confluent necrosis, and central venulitis without true venoocclusive changes may be observed. Microgranulomas are common in cases of DILI due to allopurinol and phenytoin. Fibrin ring granulomas have been described in allopurinol-related DILI, but this is a nonspecific finding that can be seen in Q fever, hepatitis A, leishmaniasis, and Hodgkin lymphoma.

Acute and Chronic Cholestasis/Mixed Hepatocellular-Cholestatic Injury

The acute or intrahepatic cholestatic pattern is defined as hepatocellular or canalicular bile stasis (or both) in the absence of marked inflammation. If intrahepatic cholestasis is associated with one of the necroinflammatory patterns described for hepatocellular injury, the pattern is categorized as *mixed hepatocellular-cholestatic injury* or *cholestatic hepatitis*. Bile duct injury is usually present, although pronounced duct loss suggests a chronic disorder such as primary biliary cirrhosis, primary sclerosing cholangitis, or vanishing bile duct syndrome. The combination of cholestasis with inflammation and hepatic injury is a common histologic pattern of injury in DILI.

Examples of Drugs Associated With DILI

Acetaminophen

The most common cause of acute liver failure in the United States and Europe is acetaminophen toxicity. The metabolism of acetaminophen is shown in Figure 31.2. Decreases in glutathione in patients with chronic liver disease predispose to the production of the toxic metabolite. Also, patients with chronic excessive intake of alcohol produce more of the toxic intermediate because of the induction of CYP2E1 activity.

Acetaminophen hepatotoxicity is characterized by very high levels of aminotransferases (often >5,000 U/L). Renal failure is also common. The degree of increase in the AST level at the time of presentation following an acetaminophen overdose is helpful in predicting hepatotoxicity. Hepatotoxicity rarely develops in patients with AST levels less than 50 U/L at presentation, whereas 16% of those with AST levels more than 1,000 U/L at presentation die or need liver transplant. Patients with acetaminophen hepatotoxicity and poor prognostic markers should be hospitalized and their condition monitored. The King's College criteria for liver transplant are listed in Box 22.2 in Chapter 22. When *N*-acetylcysteine is administered soon after acetaminophen has been ingested, it acts by enhancing the conjugation and, thus, the water solubility and excretion of *N*-acetyl-*p*-quinone imine. When administered later, after liver injury has developed, *N*-acetylcysteine acts by antioxidant and antiinflammatory mechanisms that are not well understood. *N*-acetylcysteine also may enhance liver perfusion through inotropic and vasodilatory effects. Although the efficacy of *N*-acetylcysteine diminishes when it is given more than 8 hours after acetaminophen has been ingested, it nonetheless should be administered up to 24 hours after ingestion because of its putative hepatoprotective effects.

Antibiotics

The drug class that most commonly causes nonfulminant liver injury is antibiotics. Amoxicillin-clavulanic acid is the most frequently reported antibiotic that causes hepatotoxicity. Liver injury usually manifests within 1 to 4 weeks after treatment with the drug has been stopped, but it can occur even later. The clinical presentation of patients with DILI can be either hepatocellular or cholestatic. Similar to other forms of drug-induced cholestatic liver injury, the cholestasis due to amoxicillin-clavulanic acid may take weeks or months to resolve. Other "classic" antibiotics associated with DILI are nitrofurantoin, minocycline, isoniazid, trimethoprim-sulfamethoxazole, erythromycin, and the fluoroquinolones. Telithromycin, a ketolide antibiotic, has been reported to cause severe hepatotoxicity, including the development of ascites. In 2007, the FDA required a label change and a boxed warning about hepatotoxicity.

The NIH DILIN series has also reported on 12 cases of fluoroquinolone-related DILI, of which 7 had features of hypersensitivity. The biochemical pattern of liver injury was evenly split between hepatocellular, mixed, and cholestatic types. The median latency was 2.5 days. Serious outcomes occurred: 3 patients had hepatic or other organ failure, 1 patient required liver transplant for vanishing bile duct syndrome, and another died of acute liver failure.

Antiretroviral Agents

Drugs against the human immunodeficiency virus cause hepatotoxicity in 2% to 18% of patients. Most episodes of DILI are asymptomatic, and in most cases, increases in ALT levels resolve spontaneously.

Of the protease inhibitors, ritonavir (especially at high doses) carries the highest risk of liver toxicity, with an incidence of 3% to 9%. The newer protease inhibitor tipranavir has been associated with severe hepatotoxicity, especially when used in combination with ritonavir and particularly in patients with hepatitis B or C.

Newer nucleoside reverse transcriptase inhibitors, such as emtricitabine, abacavir, and tenofovir, are associated with a low

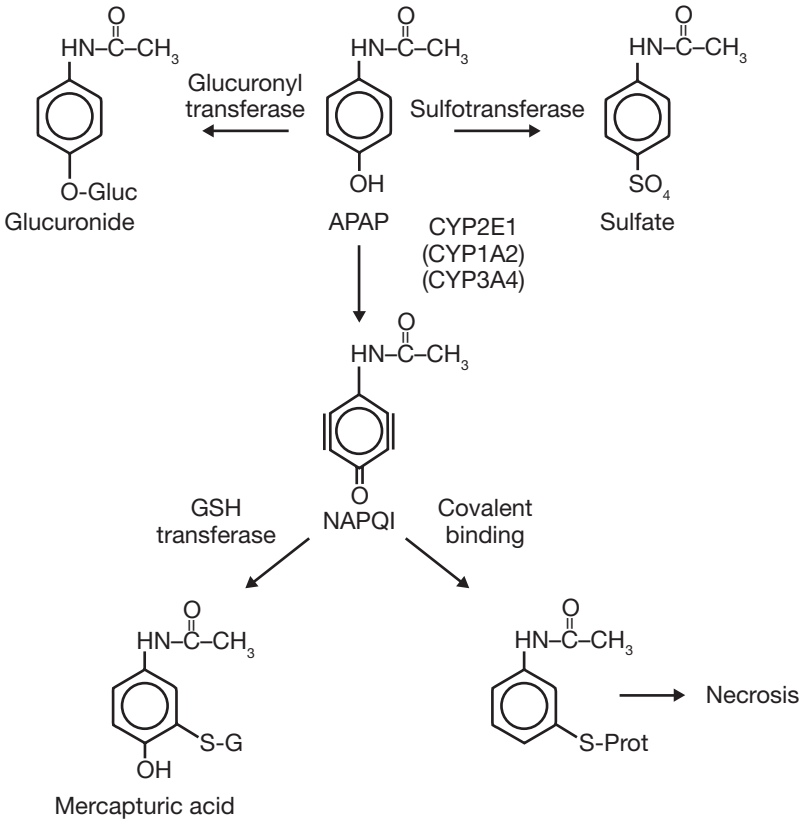

Figure 31.2. Metabolism of Acetaminophen (APAP). Most APAP is conjugated to either glucuronide or sulfate. The portion that is oxidized to *N*-acetyl-*p*-benzoquinone imine (NAPQI) is further detoxified by glutathione (GSH) transferase. If this system is overwhelmed, NAPQI binds to cellular targets, leading to hepatocellular necrosis. CYP indicates cytochrome P450. (Adapted from Zimmerman HJ. Acetaminophen hepatotoxicity. Clin Liver Dis. 1998 Aug;2[3]:523-41. Used with permission.)

incidence of increased ALT levels. The major toxic effect of nucleoside reverse transcriptase inhibitors (especially didanosine and stavudine) is lactic acidosis due to mitochondrial toxicity, which generally occurs after several weeks or months of treatment. Histologic examination of the liver usually shows steatosis, and the mortality rate is high. Among patients with hepatitis C, the administration of ribavirin to those also receiving didanosine or stavudine has been associated with mitochondrial toxicity.

A hypersensitivity DILI reaction due to the nonnucleoside reverse transcriptase inhibitor nevirapine occurs in 2.3% of patients and has also been seen with abacavir and efavirenz. This form of liver injury tends to develop within a few weeks after the start of therapy. A different pattern of drug injury has emerged with the use of nevirapine: Liver enzyme levels begin to increase after more than 16 weeks of therapy, consistent with direct or idiosyncratic host-mediated liver injury. Patients who have chronic viral hepatitis are likely at increased risk for toxicity with nevirapine therapy. In a large group of 8,851 patients studied by the AIDS Clinical Trials Group, baseline elevations of aminotransferases, hepatitis C, and regimens containing didanosine or nevirapine were associated with severe hepatoxicity.

Herbal and Dietary Supplements

Herbal and dietary supplements are commonly used in the United States and throughout the world. The clinical patterns of presentation and severity of hepatotoxicity associated with these supplements can be highly variable, even for the same product. Box 31.3 lists some of the most common herbal and dietary supplements associated with DILI. The FDA assigned warnings to several Hydroxycut (Iovate Health Sciences, Inc) and Herbalife (Herbalife International of America, Inc) products on the basis of documented reports of severe liver injury, transplant, and death associated with these compounds. Hydroxycut products were recalled, and new formulations were released.

According to the NIH DILIN prospective study, herbal and dietary supplements were implicated in approximately 10% of consecutively enrolled cases of DILI. Furthermore, in the Spanish registry, 2% of cases of DILI were attributed to herbal remedies or dietary supplements. In Asian countries, the proportion of DILI caused by herbal supplements can be as high as 19% to 63%.

Herbal and dietary supplements should be considered in the differential diagnosis of liver injury. Many patients do not consider over-the-counter, nutritional, or herbal supplements as medicine; thus, these agents may not be included when patients are asked about medicines taken before the episode of liver injury. Careful, repeated, and directed questioning is required.

Lipid-Lowering Agents

Because of the frequency with which statins are prescribed, there has been much interest in the potential liver toxicity of these agents. Determining whether patients receiving statins have DILI is difficult because mild increases in liver enzyme levels are common within 1 month after the initiation of statin therapy, but the

Box 31.3. Selected Herbal and Dietary Supplements Associated With Hepatoxicity

Aloe vera

Atractylis gummifera

Black cohosh

Callilepsis laureola (impila)

Camphor oil

Cascara (cascara sagrada)

Centella asiaticus (gotu kola)

Chaparral (*Larrea tridentata*)

Dai-saiko-to (Sho-saiko-to, TJ-19, Da-Chai-Hu-Tang, Xiao-Chai-Hu-Tang)

Geniposide (*Gardenia jasminoides*)

Germander (*Teucrium chamaedrys* and other *Teucrium* species)

Greater celandine (*Chelidonium majus*)

Green tea (*Camellia sinensis*)

Herbalife products[a]

Hydroxycut products[b] (first-generation formulation production was halted in 2009)

Jin bu huan (*Lycopodium serratum*)

Kava (*Piper methysticum*)

Ma huang (*Ephedra sinica*)

Mistletoe (*Viscum album*)

Noni juice (*Morinda citrifolia*)

Pennyroyal (squawmint oil)

Pyrrolizidine alkaloids (*Crotalaria, Heliotropium, Senecio, Symphytum* [comfrey])

Saw palmetto (*Serenoa repens*)

Senna (*Cassia angustifolia* and *Cassia acutifolia*)

Skullcap (*Scutellaria*)

Valerian (*Valeriana officinalis*)

[a] Herbalife International of America, Inc.

[b] Iovate Health Sciences, Inc.

levels nearly always improve despite continued administration of these agents. Furthermore, mildly fluctuating liver enzyme levels occur also in hyperlipidemic patients not receiving statin therapy. The presence of nonalcoholic fatty liver disease in many patients who are candidates for statin therapy further confounds the issue, although it has been well demonstrated that statin drugs are safe for patients with nonalcoholic fatty liver disease.

Serious DILI from statin agents is rare. The risk of acute liver failure associated with lovastatin, the first of the statins to be approved for treatment of hypercholesterolemia, is about 1 in 1 million patient-treatment years. From 1990 to 2002, only 3 of more than 51,000 liver transplants in the United States were performed for presumed statin-induced liver injury. In a study from Sweden (1998-2010), 73 cases of DILI from statins were identified; 19% were considered probable, and 10% highly probable. One patient required liver transplant, and 2 patients died. The median latency was 3 months. Patients taking atorvastatin were more likely to present with a cholestatic or mixed profile (57%) compared with patients taking simvastatin (25%). Although atorvastatin and simvastatin were the most frequent culprits responsible for DILI, patients taking fluvastatin had the highest incidence of DILI compared with patients taking any other statin. The incidence of DILI from statins was estimated to be 1.6 per 100,000 person-years.

The FDA labeling for statins has changed. Patients should have baseline liver tests before treatment is initiated. Routine posttreatment monitoring is not recommended, although symptoms, such as jaundice, that suggest liver disease should be investigated with liver tests. Statins rarely have been associated with the development of autoimmune hepatitis, although the association may be only coincidental.

Ezetimibe, which blocks the intestinal absorption of cholesterol, has been associated with increased liver enzyme levels and, when administered in combination with statins, may rarely cause clinically significant hepatoxicity. Sustained-release niacin also may produce symptomatic hepatotoxicity.

Tumor Necrosis Factor α Antagonists

In the NIH DILIN study, 6 patients who had DILI from tumor necrosis factor antagonists were evaluated with 28 other cases from the DILI literature. All reported cases were caused by infliximab (n = 26), adalimumab (n = 4), and etanercept (n = 4). Interestingly, 67% of patients had positive autoantibodies, and for 15 of 17 patients who underwent liver biopsy, the histologic findings included autoimmune features. The median latency was 13 weeks, but patients with autoimmune features tended to present later than those without. Most cases of DILI were either mild or moderate; 1 patient with preexisting cirrhosis required liver transplant.

Treatment

For most patients with DILI, treatment is based on withdrawal of the agent and general support. For acetaminophen toxicity, *N*-acetylcysteine should be given. Carnitine may be helpful for valproate-induced microvesicular steatosis. Drug-induced autoimmune hepatitis that does not improve spontaneously can be treated with corticosteroids.

Recently, the US Acute Liver Failure Study Group reported the results of a randomized controlled trial examining intravenous *N*-acetylcysteine for the treatment of acute liver failure from causes other than acetaminophen. In this prospective, double-blind trial, patients with acute liver failure (nonacetaminophen) were randomly assigned to receive *N*-acetylcysteine or placebo infusion for 72 hours. Patients with acute liver failure caused by DILI (n=45) represented the single largest group among the 173 patients. Although the overall survival at 3 weeks was not

significantly different between the groups, transplant-free survival was significantly better for patients in the *N*-acetylcysteine group (40% vs 27%, *P*=.43). The benefits of *N*-acetylcysteine were seen primarily in patients with early-stage disease and coma grade I or II (52% vs 30% transplant-free survival), but not in those with advanced coma grade (III or IV) at randomization. When the overall and transplant-free survival of the 4 largest etiologic groups was considered, patients with DILI and hepatitis B virus infection showed improved outcome compared with patients in the autoimmune hepatitis and indeterminate groups. For the DILI patients, the transplant-free survival was 58% for those receiving *N*-acetylcysteine and 27% for those receiving placebo. The study results suggest that therapy with intravenous *N*-acetylcysteine should be considered for patients with acute liver failure due to idiosyncratic DILI.

Compared with hepatocellular drug injury, cholestatic liver injury is less likely to be serious but more likely to be prolonged. Ursodiol has been used in cases of drug-induced cholestasis, with a prolonged recovery phase. Responses have been reported, but the lack of controlled data makes it difficult to draw conclusions about the efficacy of ursodiol.

Prognosis

The prognosis for patients with DILI varies. According to the Hy rule (named after the hepatologist Hyman Zimmerman), patients with jaundice due to drug-induced hepatocellular injury have a 10% mortality rate without transplant even if treatment with the drug is discontinued promptly. This rule has been confirmed by recent studies from Spain, Sweden, and the United States that reported mortality rates between 9% and 12% for patients with hepatocellular jaundice. Patients with acute liver failure due to idiosyncratic drug injury have an 80% mortality rate without transplant. Thus, patients who have hepatocellular DILI and jaundice in whom encephalopathy or coagulopathy develops should be referred for consideration of liver transplant.

Whether chronic DILI will develop after a patient recovers from an acute injury is not clear. Most patients with DILI who survive have complete biochemical and histologic recovery. Yet, a small proportion of patients may have chronically increased serum levels of liver enzymes that may signify chronicity. A recent follow-up study of DILI patients from Sweden (mean duration of follow-up, 10 years) concluded that the development of clinically important liver disease after severe DILI was highly uncommon. A prospective follow-up of DILI patients in the Spanish hepatotoxicity registry showed a 5% incidence of chronic DILI; in comparison, 14% of patients in the NIH DILIN study had persistent laboratory test result abnormalities. The most recent data from Iceland showed chronicity in 7% of patients. Further study is needed to determine the frequency and impact of chronic DILI.

Pharmacogenetics

There is considerable interest in identifying the genes that contribute to DILI. Before the year 2000, little information was available on genetic susceptibility to DILI. However, both genome-wide association and candidate gene studies have recently confirmed an important role for HLA class I and class II genes in some but not all forms of DILI. A recently identified association between DILI due to flucloxacillin and the HLA-B*5701 allele is, to date, the strongest reported association between any gene and DILI (odds ratio, 80). The second replicated HLA association is between amoxicillin-clavulanate–related DILI and the HLA class II allele DRB1*1501. Also, evidence for the association between a polymorphism in the gene encoding *N*-acetyltransferase 2 (*NAT2*), an enzyme important in isoniazid metabolism, and susceptibility to DILI has been confirmed. Persons who have *NAT2* variants associated with slow acetylation appear to have an increased risk of isoniazid-related DILI.

However, not all genetic effects relevant to DILI will necessarily be of the magnitude identified in genome-wide association studies, and larger studies may be needed to detect genes with smaller effects. Emerging techniques, such as whole-genome sequencing, will be needed for further progress in this area of study.

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32

Autoimmune Hepatitis[a]

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Autoimmune hepatitis is a self-perpetuating inflammation of the liver of unknown cause that is associated with autoantibodies, hypergammaglobulinemia, and interface hepatitis seen on histologic examination. Autoimmune hepatitis afflicts 100,000 to 200,000 persons in the United States annually and accounts for 5.9% of liver transplants performed in the United States. Among white northern Europeans, the mean annual incidence of autoimmune hepatitis is 1.9 per 100,000, and the point prevalence is 16.9 per 100,000. Autoimmune hepatitis occurs more commonly in women (female to male ratio, 3.6:1), and it affects all ages, including infants.

Originally described in white northern Europeans and North Americans, autoimmune hepatitis is now recognized to occur worldwide. Ethnic background may affect the clinical presentation: African American patients have a higher frequency of cirrhosis at presentation than white North Americans; Alaskan natives have a higher occurrence of acute icteric disease than nonnative patients; Arab patients have cholestatic features; Asian patients tend to have late-onset, mild disease; South American patients are commonly young children with severe disease; and Somali patients are usually men with cholestatic features and a poor response to corticosteroid treatment. These findings suggest that differences in genetic predisposition or regional differences in etiologic agents may affect the clinical phenotype.

Etiology

The cause of autoimmune hepatitis is unknown. Multiple agents have been implicated as triggers of the disease, including certain viruses (hepatitis A, hepatitis B, hepatitis C, Epstein-Barr, herpes simplex, and measles viruses) and drugs (minocycline, diclofenac, isoniazid, α-methyldopa, nitrofurantoin, propylthiouracil, and atorvastatin; recently, infliximab and adalimumab have been implicated). Hepatitis A virus infection (and hepatitis A vaccine) and minocycline have been implicated most often worldwide. Herbal products that are marketed as "immune stimulating" as well as other herbal agents, including black cohosh, khat, and Chinese herbal teas, may precipitate autoimmune hepatitis. Most cases have no identifiable trigger.

Triggers may share epitopes that resemble self-antigens, and they may break self-tolerance by overcoming antigenic ignorance, mimicking sequestered epitopes, or generating neoepitopes (or a combination of these). Molecular mimicry between foreign antigens and self-antigens is the most frequently proposed initiating mechanism. Efforts to identify an etiologic basis are complicated by the long lag time between antigenic exposure and disease expression and by the persistence of disease after the disappearance of the triggering event. Repeated exposures to the triggering antigen, in turn, may trigger autoreactive responses

[a] Portions of this chapter were adapted from Al-Khalidi JA, Czaja AJ. Current concepts in the diagnosis, pathogenesis, and treatment of autoimmune hepatitis. Mayo Clin Proc. 2001 Dec;76(12):1237-52; Czaja AJ. Clinical features, differential diagnosis and treatment of autoimmune hepatitis in the elderly. Drugs Aging. 2008;25(3):219-39; and Makol A, Watt KD, Chowdhary VR. Autoimmune hepatitis: a review of current diagnosis and treatment. Hepat Res Treat. 2011;2011:390916. Epub 2011 May 15. Used with permission.

Abbreviations: ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; anti-ASGPR, asialoglycoprotein receptor antibody; anti-LC1, liver cytosol type 1 antibody; anti-LKM1, liver-kidney microsomal antibody type 1; anti-SLA, soluble liver antigen antibody; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; AST, aspartate aminotransferase; pANCA, perinuclear antineutrophil cytoplasmic antibody; SMA, smooth muscle antibody; ULRR, upper limit of the reference range

against the liver and anatomically distant organs, thereby causing not only autoimmune hepatitis but concurrent immune diseases.

Diagnosis

An international panel has codified the diagnostic criteria. Definite diagnosis requires the exclusion of hereditary conditions (Wilson disease, hereditary hemochromatosis, and alpha$_1$-antitrypsin deficiency), viral infections (hepatitis A, B, and C virus infections), and drug-induced conditions (related to minocycline, diclofenac, isoniazid, propylthiouracil, α-methyldopa, or nitrofurantoin). Table 32.1 is a simplified (more clinically relevant) version of the diagnostic criteria for probable and definite autoimmune hepatitis.

The 6-month requirement to establish chronicity has been waived because an acute, rarely fulminant presentation has been recognized that may resemble acute viral or toxic hepatitis. A marked increase (>2-fold the upper limit of the reference range [ULRR]) in the serum alkaline phosphatase level or the presence of pruritus suggests another diagnosis. Celiac disease can be associated with a liver disease that resembles autoimmune hepatitis, and it should be excluded in patients.

Interface hepatitis is the histologic hallmark of autoimmune hepatitis (Figure 32.1). The morphologic pattern is nonspecific and occurs in acute and chronic liver diseases of diverse causes. Plasma cell infiltration of the hepatic parenchyma or portal tracts (or both) is apparent in 66% of tissue specimens, but its presence is neither specific nor required for the diagnosis (Figure 32.2). A lobular, or panacinar, hepatitis frequently accompanies interface hepatitis, and a centrilobular (zone 3) necrosis has also been described. Successive examinations of liver tissue have shown transition of the centrilobular (zone 3) necrosis to interface hepatitis, and it may be an early form of the disease.

A scoring system that grades individual components of the syndrome provides an objective means to assess the strength of the diagnosis, accommodate unusual features, and compare populations in different geographic regions and treatment trials (see the article by Alvarez et al in the Suggested Reading list). The scoring system has been developed as a research tool to ensure homogeneous populations in research studies; it usually is not needed for a confident clinical diagnosis. A simplified scoring system has been developed to ease clinical application, and it has a sensitivity of 88% and a specificity of 97% for autoimmune hepatitis (Table 32.1).

Table 32.1. Diagnostic Criteria for Autoimmune Hepatitis (AIH)

Variable	*Points*[a]
ANA or SMA ≥1:40	1
ANA or SMA ≥1:80 *or* Anti-LKM1 ≥1:40 *or* Anti-SLA positive	2[b]
IgG >1×ULRR	1
IgG >1.10×ULRR	2
Histology *compatible with* AIH	1
Histology *typical of* AIH	2
Absence of viral hepatitis	2

Abbreviations: ANA, antinuclear antibody; anti-LKM1, antibody to liver-kidney microsome type 1; anti-SLA, antibody to soluble liver antigen; SMA, smooth muscle antibody; ULRR, upper limit of the reference range.
[a] Score ≥6 points = probable AIH (sensitivity, 88%; specificity, 97%). Score ≥7 points = definite AIH (sensitivity, 81%; specificity, 99%).
[b] Maximum of 2 points for all autoantibodies.
Data from Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, et al; International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008 Jul;48(1):169-76.

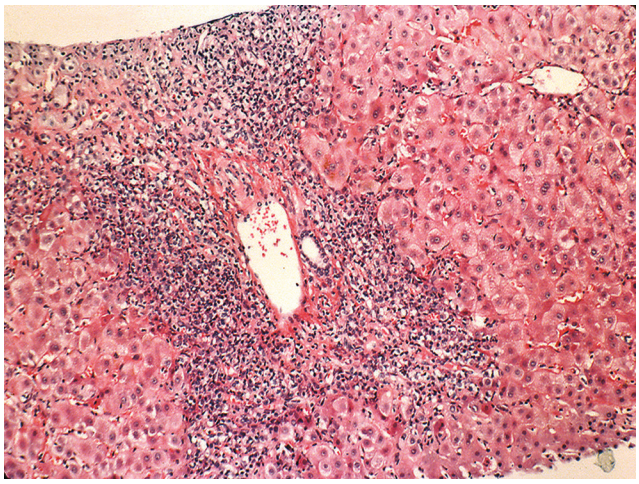

Figure 32.1. Interface Hepatitis. The limiting plate of the portal tract is disrupted by an inflammatory infiltrate that extends into the acinus. Interface hepatitis is a requisite for the diagnosis of autoimmune hepatitis, but it is not specific for the diagnosis (hematoxylin-eosin, original magnification ×200). (Adapted from Czaja AJ. Current concepts in autoimmune hepatitis. Ann Hepatol. 2005 Jan-Mar;4[1]:6-24. Used with permission.)

Clinical Features

Women constitute at least 70% of cases, and 50% are younger than 40 years (Table 32.2). Onset is usually between the third and fifth decades, but the age at onset may range from infancy to extremely elderly. Autoimmune hepatitis tends to be more severe in children than in adults. Children commonly have cirrhosis at

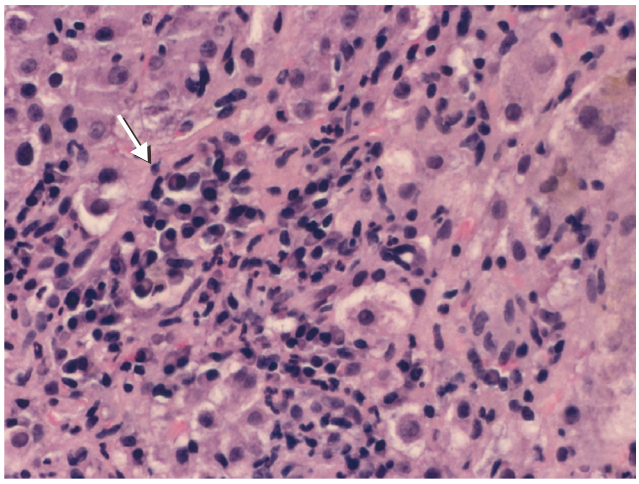

Figure 32.2. Plasma Cell Infiltration of the Hepatic Parenchyma. Plasma cells (arrow) are characterized by a cytoplasmic halo adjacent to a deeply basophilic nucleus. Plasma cells typically are abundant at the interface and throughout the acinus, but they do not have diagnostic specificity (hematoxylin-eosin, original magnification ×400). (Adapted from Czaja AJ. Current concepts in autoimmune hepatitis. Ann Hepatol. 2005 Jan-Mar;4[1]:6-24. Used with permission.)

Table 32.2. Typical Features of Autoimmune Hepatitis

Feature	*Patients, %*
Clinical features	
Female sex	70
Younger than 40 y	50
Acute onset	40
Asymptomatic	25-34
Common symptoms	
Fatigue	85
Arthralgia	30
Myalgia	30
Develop later, after asymptomatic presentation	26-70
Frequent physical findings	
Normal	80
Hepatomegaly	20
Typical laboratory findings	
Increased serum levels of AST and ALT	100
Increased serum of γ-globulin and IgG	90
Mild hyperbilirubinemia (bilirubin <3 mg/dL)	83
Serum alkaline phosphatase increased <2-fold ULRR	67
ANA, SMA, or anti-LKM1	87

Abbreviations: ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-LKM1, antibody to liver-kidney microsome type 1; AST, aspartate aminotransferase; SMA, smooth muscle antibody; ULRR, upper limit of the reference range.

presentation (as many as 50%), and, during therapy, they enter a sustained remission less often than adults, especially if they have antibodies to liver-kidney microsome type 1 (anti-LKM1). Cholangiographic abnormalities that have been designated as *autoimmune sclerosing cholangitis* can occur in children, and they may not be accompanied by cholestatic features, inflammatory bowel disease, or refractoriness to corticosteroid treatment. In contrast, adults with autoimmune hepatitis and similar cholangiographic findings typically have inflammatory bowel disease and a poor response to corticosteroid therapy.

Compared with young adult patients, elderly patients more commonly have cirrhosis at presentation and concurrent thyroid disorders (Graves disease or autoimmune thyroiditis) or rheumatic disorders (rheumatoid arthritis, Sjögren syndrome, or systemic lupus erythematosus). Elderly white patients from North America or northern Europe have HLA-DRB1*04 more often and HLA-DRB1*03 less often than young adult patients with a similar ethnic background, and they respond well to corticosteroid therapy. These findings suggest that triggering events in elderly patients are different from those in young adults or that their genetic phenotype is associated with a less vigorous immune response.

Onset of symptoms is abrupt in 40% of patients, and a fulminant presentation is possible, especially in the young. Autoimmune hepatitis also may have an indolent clinical course that exacerbates spontaneously and resembles acute hepatitis. Features of chronic liver disease that are common in these patients include hypergammaglobulinemia and fibrosis or cirrhosis seen on histologic examination. In others with an acute presentation, the findings are indistinguishable from those of severe acute hepatitis; the histologic features include interface and lobular hepatitis without fibrosis or cirrhosis. The acute severe and fulminant manifestations of autoimmune hepatitis are important to recognize because the institution of corticosteroid therapy can be beneficial in 36% to 100% of these patients.

Autoimmune hepatitis is asymptomatic in 25% to 34% of patients at presentation. Symptomatic and asymptomatic patients have similar histologic features, including the occurrence of cirrhosis. Many asymptomatic patients (26%) have inactive cirrhosis, and their survival is not enhanced with corticosteroid treatment. Similarly, asymptomatic patients without cirrhosis who have mild inflammatory activity can have 10-year life expectancies that exceed 80% without treatment. In these instances, the absence of symptoms is associated with stable inactive or minimally active disease, and treatment is not warranted. Asymptomatic patients commonly become symptomatic (26%-70%), though, and they must be monitored regularly for progressive disease activity. The absence of symptoms is not a justification for withholding treatment from patients who otherwise have active disease.

Symptomatic patients typically have easy fatigability. Other symptoms include myalgias, arthralgias, anorexia, jaundice or dark urine, and, less commonly, cosmetic changes (facial rounding, hirsutism, or acne), delayed menarche or amenorrhea, obscure fever (rarely as high as 40°C), and right upper quadrant discomfort. Pruritus and weight loss are unusual, and they suggest an alternative diagnosis or a disease complicated by biliary obstruction or hepatocellular cancer.

Physical Findings

Most patients with autoimmune hepatitis have normal physical examination findings despite severe inflammatory activity (Table 32.2). Hepatomegaly is the most common physical finding. Ascites and hepatic encephalopathy are indicative of advanced liver disease and cirrhosis, and they usually are not noted at presentation. The clinical features of acne, hirsutism, obesity, and amenorrhea in young women that originally constituted the syndrome of lupoid hepatitis are now rarely seen.

Laboratory Features

Abnormalities in serum aminotransferase levels are essential for the diagnosis of autoimmune hepatitis (Table 32.2). The serum γ-globulin level is typically, but not invariably, increased, and the diagnosis is suspect without this finding. The serum γ-globulin level is usually polyclonal, and the predominant elevation is the serum IgG level. The importance of the serum IgG level in diagnosing autoimmune hepatitis is evident by its importance in the simplified diagnostic scoring system (Table 32.1). Approximately 25% of patients with type 2 autoimmune hepatitis have normal serum immunoglobulin levels.

In most instances, the serum aminotransferase level at presentation does not exceed 500 U/L (range, 150 U/L to >1,000 U/L), and the γ-globulin level ranges from 2 to 3 g/dL. Hyperbilirubinemia is present in 83% of patients with severe inflammatory activity, but the serum bilirubin concentration exceeds 3 mg/dL in only 46%. Similarly, an abnormal increase in the serum level of alkaline phosphatase can be demonstrated in 81% of patients, but it is more than 2-fold the ULRR in only 33% and more than 4-fold the ULRR in only 10%.

HLA-DRB1*03, HLA-DRB1*04, and a combination of both are the principal risk factors for autoimmune hepatitis in white North American and northern European patients, and they are found in 85% of cases. HLA-DRB1*03 is associated with early-age onset, diminished response to corticosteroids, and frequent requirement for liver transplant. HLA-DRB1*04 is associated with disease onset at age 45 years or older, female sex, and frequent concurrent immune diseases. HLA typing has *not* been endorsed as a diagnostic or prognostic tool, but it may prove

useful in determining etiologic factors and populations at risk for the disease.

Autoantibodies

Antinuclear antibody (ANA), smooth muscle antibody (SMA), and anti-LKM1 are the serologic markers of autoimmune hepatitis, and they should be measured in all patients with suspected disease. They are not pathogenic, and serum titers do not have prognostic significance. Low titers should not dissuade a clinician from the diagnosis if other features implicate the disorder. The conventional autoantibodies may not be present in some patients at presentation but may be detected later in the disease course; serum titers can fluctuate during the course of illness. No specific pattern of ANA has been identified, but a homogenous pattern is more common. SMA is more specific to autoimmune hepatitis and is seen alone (30%-35% of type 1 autoimmune hepatitis) or in combination with ANA (55%-60% of type 1 autoimmune hepatitis). Anti-LKM1 is associated with type 2 autoimmune hepatitis and is directed toward the cytochrome P450 2D6 isozyme.

Another autoantibody that supports the diagnosis of autoimmune hepatitis and whose assay generally is available is perinuclear antineutrophil cytoplasmic antibody (pANCA), which occurs in 50% to 90% of patients with type 1 autoimmune hepatitis. pANCA may be useful in the evaluation of seronegative ("cryptogenic") chronic hepatitis. In this same fashion, IgA antibody to tissue transglutaminase or endomysium is useful for excluding liver disease associated with celiac disease.

Antibodies that have not been incorporated into a conventional diagnostic algorithm are antibodies to actin (anti-actin, commonly associated with the presence of SMA), soluble liver antigen (anti-SLA), asialoglycoprotein receptor (anti-ASGPR), chromatin, and liver cytosol type 1 (anti-LC1, frequently associated with anti-LKM1). Anti-ASGPR, anti-chromatin, and anti-SLA are associated with relapse after treatment withdrawal, and anti-actin, anti-SLA, and anti-LC1 identify young patients who have aggressive disease. Cryptogenic chronic hepatitis may be reclassified as autoimmune hepatitis by subsequent testing for the conventional autoantibodies or by testing for the nonstandard markers (pANCA or anti-SLA).

Antimitochondrial antibody (AMA), including antibody against the M2 antigens associated with primary biliary cirrhosis, is found in 8% to 20% of patients with autoimmune hepatitis. Assays based on indirect immunofluorescence may mistake anti-LKM1 for AMA because the diagnostic patterns of indirect immunofluorescence on the murine kidney tubule can be confused. Other patients may have an overlap syndrome with primary biliary cirrhosis, early-stage primary biliary cirrhosis, or coincidental collateral autoantibody production. In patients with otherwise classic autoimmune hepatitis, AMA has not affected treatment response.

ANA and SMA can occur in acute and chronic hepatitis of diverse causes, including alcoholic liver disease, nonalcoholic fatty liver disease, and viral hepatitis. They are usually low titer, background reactivities that should not alter diagnosis or management. The anti-LKM1 found in as many as 10% of European patients with chronic hepatitis C is different from the anti-LKM1 found in patients with classic autoimmune hepatitis. Autoantibodies, regardless of titer or type, expand the differential diagnosis, but they alone never establish the true diagnosis of the disease.

Concurrent Immune Diseases

Concurrent immune diseases are present in 30% to 48% of patients with autoimmune hepatitis (Box 32.1). Autoimmune thyroiditis, synovitis, and ulcerative colitis are the most common concurrent immune diseases. Of the patients who have autoimmune hepatitis and ulcerative colitis, 59% have normal cholangiograms and a good response to corticosteroid treatment. The other 41% have

Box 32.1. Immune Diseases Associated With Autoimmune Hepatitis

- Autoimmune sclerosing cholangitis[a]
- Autoimmune thyroiditis[b]
- Celiac disease
- Coombs-positive hemolytic anemia
- Cryoglobulinemia
- Dermatitis herpetiformis
- Erythema nodosum
- Fibrosing alveolitis
- Focal myositis
- Gingivitis
- Glomerulonephritis
- Graves disease[b]
- Idiopathic thrombocytopenic purpura
- Intestinal villous atrophy
- Iritis
- Lichen planus
- Myasthenia gravis
- Neutropenia
- Pericarditis
- Peripheral neuropathy
- Pernicious anemia
- Pleuritis
- Pyoderma gangrenosum
- Rheumatoid arthritis[b]
- Sjögren syndrome
- Synovitis[b]
- Systemic lupus erythematosus
- Type 1 diabetes mellitus[a]
- Ulcerative colitis[b]
- Urticaria
- Vitiligo[a]

[a] Mainly in children.

[b] Most common associations.

Adapted from Czaja AJ. Autoimmune liver disease. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. Vol 2. 4th ed. Philadelphia (PA): Saunders; c2003. p. 1163-202. Used with permission.

Table 32.3 Comparison of Types 1 and 2 Autoimmune Hepatitis

	Autoimmune Hepatitis	
Feature	*Type 1*	*Type 2*
Characteristic autoantibodies	ANA, SMA	Anti-LKM1
Associated autoantibodies	pANCA	Anti-LC1
	Anti-SLA	Anti-ASGPR
	Anti-actin	Anti–parietal cell
	Anti-ASGPR	
Age at onset	Any age	Mainly pediatric (2-14 y)
Common concurrent immune diseases	Autoimmune thyroiditis	Vitiligo
	Synovitis	Type 1 diabetes mellitus
	Ulcerative colitis	Autoimmune thyroiditis
Implicated genetic factors	*DRB1*0301* (northern Europe)	*DQB1*02*
	*DRB1*0401* (northern Europe)	*DRB1*03* (anti-LKM1)
	*DRB1*1501* (protective)	*DRB1*07* (anti-LC1)
	*DRB1*1301* (South America)	
Autoantigen	Uncertain	CYP2D6
Treatment	Corticosteroids	Corticosteroids

Abbreviations: ANA, antinuclear antibody; anti-ASGPR, antibody to asialoglycoprotein receptor; anti-LC1, antibody to liver cytosol type 1; anti-LKM1, antibody to liver-kidney microsome type 1; anti-SLA, antibody to soluble liver antigen; CYP2D6, cytochrome P450 2D6; pANCA, perinuclear antineutrophil cytoplasmic antibody; SMA, smooth muscle antibody.
Adapted from Czaja AJ. Autoimmune liver disease. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. Vol 2. 4th ed. Philadelphia (PA): Saunders; c2003. p. 1163-202. Used with permission.

primary sclerosing cholangitis and no response to corticosteroid treatment. Autoimmune hepatitis is present in 15% of patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).

Subclassifications

Two types of autoimmune hepatitis (types 1 and 2) have been proposed on the basis of serologic markers (Table 32.3). The International Autoimmune Hepatitis Group has not endorsed these subclassifications because each type lacks a specific etiologic agent, distinctive clinical behavior, or requirement for a particular treatment. Nevertheless, the designations have become useful clinical descriptors and research classifications.

Treatment Regimens

Prednisone alone or in a lower dose in combination with azathioprine is effective in the treatment of all forms of autoimmune hepatitis. Each regimen induces clinical, laboratory, and histologic remission in 65% of patients within 18 months and in 80% within 3 years (Figure 32.3). Each regimen also enhances survival expectations. The life expectancy of treated patients exceeds 80% after 20 years of observation, and it is similar to that of age- and sex-matched healthy persons from the same geographic region. Improvement in hepatic fibrosis occurs in conjunction with reductions in liver inflammation, and corticosteroids suppress inflammatory activity.

The absolute and relative indications for treatment are based on degrees of severity as assessed by clinical, laboratory, and histologic findings (Box 32.2). Patients with inactive cirrhosis (ie, minimal or no inflammation on biopsy), portal or mild interface hepatitis and no symptoms, or decompensated inactive cirrhosis with ascites, encephalopathy, or gastrointestinal tract bleeding (or a combination) do not warrant immediate immunosuppressive therapy. The diagnosis of autoimmune hepatitis does not compel the prompt institution of treatment, nor does the absence of symptoms preclude the need for therapy. Autoimmune hepatitis is by nature an aggressive liver disease with varying disease activity, and this unpredictable nature has led some to argue for treatment of all patients with the diagnosis regardless of the disease activity at presentation. The urgency rather than the need for treatment may be all that is affected by the presence of mild disease.

A preferred treatment regimen uses prednisone in combination with azathioprine (Table 32.4). The combination regimen uses a lower dose of prednisone, and it is associated with fewer corticosteroid-related side effects. It is especially useful for patients with obesity, acne, menopause, labile hypertension, brittle diabetes, emotional lability, or osteopenia (or a combination of these). The prednisone-alone regimen is useful for patients with severe, preexistent cytopenia, pregnancy or contemplation of pregnancy, or active malignancy. Both regimens are similarly effective and differ only in the frequency of adverse effects. Azathioprine has

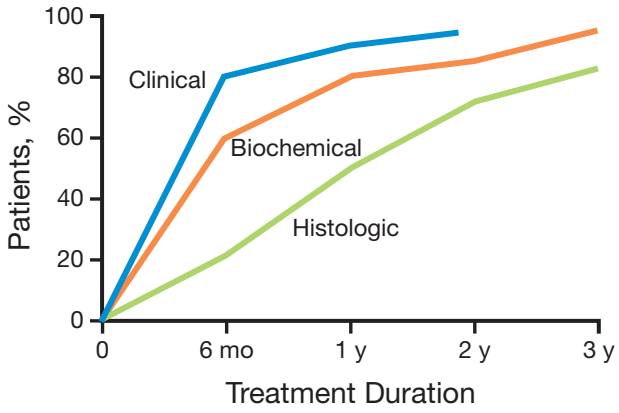

Figure 32.3. Frequencies of Clinical, Biochemical, and Histologic Remission During Conventional Corticosteroid Treatment of Autoimmune Hepatitis. Histologic improvement lags clinical and biochemical improvement by 3 to 8 months. (Data from Czaja AJ. Treatment strategies in autoimmune hepatitis. Clin Liver Dis. 2002 Aug;6[3]:799-824.)

Box 32.2. Treatment Indications for Autoimmune Hepatitis

Absolute

- Serum AST level >10-fold ULRR
- Serum AST level >5-fold ULRR and γ-globulin level >2-fold ULRR
- Bridging necrosis or multilobular necrosis in liver tissue

Relative

- Symptoms (fatigue, arthralgia, jaundice)
- Serum AST level or γ-globulin level (or both) less than for absolute criteria
- Interface hepatitis

None

- No symptoms and mild interface or portal hepatitis
- Inactive cirrhosis (ie, no inflammation on biopsy)
- Decompensated inactive or minimally active cirrhosis

Abbreviations: AST, aspartate aminotransferase; ULRR, upper limit of the reference range.

been teratogenic in animals, and it is listed as a category D drug by the US Food and Drug Administration. Although azathioprine has been used safely in transplant and inflammatory bowel disease, it has not been studied rigorously in pregnancy, its metabolites cross the placenta, and it is not essential in the treatment of autoimmune hepatitis. Autoimmune hepatitis commonly improves during pregnancy, and prednisone alone can be used to control inflammatory activity. Postpartum exacerbations are possible, and conventional dose therapy should be resumed immediately before delivery. A regimen of alternate-day corticosteroids in titrated doses has not improved histologic features, and use of this regimen has been abandoned for adults. Failure of the laboratory indices of liver inflammation and liver function to improve (especially hyperbilirubinemia) within 2 weeks after the start of corticosteroid therapy is associated with a higher early mortality rate.

Histologic improvement lags behind clinical and laboratory resolution by 3 to 8 months (Figure 32.3), and therapy should be continued for a minimum of 3 to 6 months beyond this point of improvement. Examination of a liver biopsy specimen before initial withdrawal of drug therapy is the only method for confirming histologic resolution, but biopsy is infrequently performed. Treatment often is maintained for at least 2 years before withdrawal of drug therapy is considered. The end point of treatment requires the absence of symptoms, resolution of all laboratory indices of liver inflammation, and normal liver tissue. Patients with incomplete normalization of alanine aminotransferase (ALT) levels at 6 months after diagnosis have an increased risk of an adverse liver-related outcome.

Table 32.4. Conventional Treatment Regimens

	Combination Therapy		
No. of Weeks Administered	*Prednisone, mg Daily*	*Azathioprine, mg Daily*	*Prednisone Therapy, mg Daily*
1	30	50	60
1	20	50	40
2	15	50	30
Maintenance until end point (ie, <1.5×ULRR for ALT and AST); then taper prednisone dose slowly	10	50	20

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULRR, upper limit of the reference range.

Relapse

Relapse connotes the exacerbation of disease activity after withdrawal of drug therapy, and it is characterized by an increase in serum levels of liver enzymes (ALT or aspartate aminotransferase [AST]) to at least 3-fold the ULRR. From 50% to 86% of patients have disease relapse after remission, most often during the first 6 months after the termination of therapy (50% of patients). Normalization of the serum levels of AST, γ-globulin, and IgG in conjunction with histologic resolution decreases the relative risk of relapse after drug withdrawal by 3- to 11-fold. The normalization of test results and tissue findings does not ensure a sustained remission, and 60% of patients who have achieved this result still have disease relapse up to 5 years after treatment and thus require regular follow-up testing. The high frequency of relapse should not discourage the withdrawal of drug therapy if a complete resolution of clinical, laboratory, and histologic abnormalities has been sustained. Multiple relapses and re-treatment can be associated with progression to cirrhosis, liver failure, or need for liver transplant, and a long-term maintenance regimen may be justified after the second relapse (and in certain cases, after the first relapse).

The disease is first controlled by reinstituting the original drug regimen, and then the dose of azathioprine is increased to 2 mg/kg daily as the dose of prednisone is gradually decreased and then stopped. In over 80% of patients treated in this fashion, the disease can be maintained in clinical and laboratory remission during a 10-year period. Low-dose prednisone therapy can be used also as a long-term maintenance regimen after the first relapse. This strategy requires a careful decrease in the daily maintenance dose of prednisone until the lowest level is achieved to prevent symptoms and maintain serum AST levels at less than 3-fold the ULRR.

Relapse does not preclude permanent discontinuation of medication late in the course of the disease. Among patients who have disease relapse and are re-treated, the disease eventually becomes inactive in 28%, and drug therapy can be withdrawn. The possibility of permanent withdrawal of drug therapy justifies periodic attempts at dose reduction.

Suboptimal Responses

The condition of 9% of patients deteriorates despite adherence to the drug regimen (ie, *treatment failure*); in 13% of patients, intolerable side effects develop and the patients must stop taking the medication prematurely (ie, *drug toxicity*); and 13% improve but not to a degree that satisfies remission criteria (ie, *incomplete response*). High-dose prednisone (60 mg daily) or prednisone (30 mg daily) in conjunction with higher-dose azathioprine (150 mg daily) is the treatment failure regimen that induces laboratory remission in 75% of patients within 2 years. Only 20% of patients achieve histologic remission, and patients remain at risk for progression of the disease and the development of treatment-related complications;

thus, slower tapering may be warranted but close follow-up is important. For azathioprine-intolerant patients or patients in whom treatment has failed, measurement of 6-methylmercaptopurine metabolite levels may identify those in whom allopurinol addition (with azathioprine reduction) may be of benefit, but confirmatory study is needed.

Other Treatments

Empirical therapy with cyclosporine, tacrolimus, mycophenolate mofetil, or budesonide has been used successfully in a small number of patients with drug intolerance or disease recalcitrant to conventional regimens. Cyclosporine has been administered as initial therapy, especially to children, and as salvage therapy to children and adults, but its advantage over standard regimens as first-line or rescue treatment has not been established. Similarly, tacrolimus has been used in only a small number of patients in a small number of case series (publication bias is a possibility), with high remission rates when *added to* prednisone or azathioprine (or both) (some of these patients did not have treatment-refractory disease, but instead the patients were treatment naive). Small clinical studies of mycophenolate mofetil suggest that it is an effective substitute for azathioprine, particularly in cases of azathioprine intolerance, but its effect in cases of treatment failure is less clear. Budesonide, with its first-pass metabolism, has induced complete or partial laboratory resolution in treatment-naive patients, but it has not been effective as salvage therapy for patients with severe disease for which corticosteroid therapy failed or for patients dependent on this medication. It may have a role as front-line therapy for patients with mild disease or at risk for corticosteroid-related complications. Budesonide has been associated with adverse effects in patients with cirrhosis; thus, caution must be undertaken in treating these patients. Very few data are available for other salvage agents, including sirolimus and rituximab, but anecdotal and mechanistic evidence supports their use in refractory cases.

Liver Transplant

Liver transplant is effective in the treatment of decompensated disease that is unresponsive to conventional therapies. The 5-year survival rate of patient and graft ranges from 83% to 92%, and the actuarial 10-year survival after transplant is 75%. Autoimmune hepatitis recurs in at least 17% of patients after liver transplant, and its occurrence increases with the duration of observation after transplant. Recurrent autoimmune hepatitis develops in 36% of patients after 5 years. Recurrent disease is typically mild and managed by adjustments in the immunosuppressive regimen. Autoimmune hepatitis can develop de novo in 2.5% to 3.4% of allografts of children and adults who received liver transplants for liver diseases other than autoimmune hepatitis. Treatment with prednisone and azathioprine usually is effective in suppressing disease activity.

Variant Syndromes

Patients with features of autoimmune hepatitis and another liver disease (ie, *overlap syndrome*) or findings that are similar to but atypical of classic disease (ie, *outlier syndrome*) constitute the variant syndromes. Retrospective analyses have suggested that 18% of cases of autoimmune liver disease can be reclassified as a variant form. Standardized diagnostic criteria are lacking; the natural history is uncertain; and treatment algorithms have not been validated. The principal variant syndromes are autoimmune hepatitis with features of primary biliary cirrhosis and autoimmune hepatitis with features of primary sclerosing cholangitis.

Mixed hepatitic and cholestatic features are the most important clues to the presence of a variant form. AMA, serum levels of alkaline phosphatase increased to more than 2-fold the ULRR, concurrent inflammatory bowel disease, histologic evidence of destructive cholangitis or ductopenia, and recalcitrance to corticosteroid therapy justify consideration of variant forms. Cholangiography is indicated for excluding primary sclerosing cholangitis in all adults who have autoimmune hepatitis and unexplained cholestatic clinical or biochemical features, ulcerative colitis, or refractoriness to corticosteroid treatment. Serum IgG4 should be assessed to rule out autoimmune cholangitis, but this disease is also typically steroid responsive.

Treatment is empirical and includes prednisone alone or prednisone in combination with ursodiol, with or without azathioprine. Patients with serum alkaline phosphatase levels less than twice the ULRR can experience improvement with corticosteroid therapy (with or without azathioprine). Serum alkaline phosphatase levels more than twice the ULRR and the presence of destructive cholangitis (ie, florid duct lesion) seen on histologic examination justify treatment with prednisone and ursodiol.

Features of autoimmune hepatitis can be present in chronic hepatitis C, and hepatitis C virus viremia can be present in autoimmune hepatitis. Interferon therapy for patients with autoimmune hepatitis can exacerbate the autoimmune manifestations, and corticosteroid therapy for patients with chronic hepatitis C will increase the viral load. Most patients have chronic hepatitis C and autoimmune features that should be treated in the same way as chronic viral hepatitis. Rarely, patients have classic autoimmune hepatitis, including the characteristic histologic changes, and coincidental hepatitis C virus infection. Chronic hepatitis C in these patients is probably a background finding, and corticosteroid therapy can improve the predominant autoimmune disease.

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33

Nonalcoholic Fatty Liver Disease[a]

KYMBERLY D. WATT, MD

Nonalcoholic fatty liver disease (NAFLD) refers to the accumulation of fat (mainly triglycerides) in hepatocytes that results from insulin resistance. NAFLD is recognized as the most common chronic liver disease in the Western world. NAFLD encompasses a wide spectrum of disease from bland hepatic steatosis, which is generally benign, to nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis, liver failure, and hepatocellular carcinoma. Hence, distinguishing between bland hepatic steatosis and NASH has important prognostic and management implications.

NAFLD may be categorized as primary or secondary, depending on the underlying pathogenesis (Table 33.1). Primary NAFLD, the more common type, is associated with insulin-resistant states, such as obesity, type 2 diabetes mellitus, and dyslipidemia. Other conditions associated with insulin resistance, such as polycystic ovarian syndrome and hypopituitarism, have also been described in association with NAFLD; however, the exact prevalence and significance of NAFLD in these conditions is not clear. The differentiation of primary NAFLD from secondary types is important because they have different treatments and prognoses. Primary NAFLD has reached epidemic proportions in many countries, as shown by several population-based studies. In the United States, 34% of the population 30 to 65 years old and almost 11% of the population 2 to 19 years old have hepatic steatosis. If these figures are extrapolated to the US population, more than 55 million Americans have NAFLD. The prevalence of NAFLD in the general population in the United States is almost 14-fold higher than the prevalence of hepatitis C, which affects about 4 million people. It also is almost 3-fold higher than alcohol-induced liver disease. However, this high prevalence of NAFLD contrasts with the relatively small proportion of patients with NAFLD who show evidence of disease progression or have complications of end-stage liver disease, as described below.

Clinical Manifestations

The clinical, laboratory, histologic, and diagnostic features of NAFLD are listed in Table 33.2. The majority of patients are asymptomatic. They may complain of fatigue or malaise and a sensation of fullness or discomfort in the right upper abdomen. Hepatomegaly and acanthosis nigricans are common physical findings in children, although stigmata of chronic liver disease suggestive of cirrhosis are uncommon.

The most common clinical scenario leading to the diagnosis of NAFLD is an asymptomatic increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) not due to viral hepatitis, autoimmune processes, iron overload, or alcohol abuse. Aminotransferase levels, however, are increased in only 20% of the general population with NAFLD. The AST:ALT ratio is usually less than 1:1, but this ratio increases as fibrosis advances. Fatty infiltration of the liver is detected with

[a] Portions of this chapter were adapted from Aithal GP, Das K, Chowdhury A. Epidemiology of nonalcoholic fatty liver disease (NAFLD). In: Talley NJ, Locke GR III, West JJ, Ford AC, Saito YA, editors. GI epidemiology: diseases and clinical methodology. 2nd Ed. Malden (MA): Wiley-Blackwell; c2014. pp. 430; Angulo P. Nonalcoholic fatty liver disease. In: Johnson LR, editor. Encyclopedia of gastroenterology. Vol 2. Amsterdam: Elsevier Academic Press; c2004. p. 733-6; and Watt KD. Metabolic syndrome: is immunosuppression to blame? Liver Transpl. 2011 Nov;17 Suppl 3:S38-42. Used with permission.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CT, computed tomography; MR, magnetic resonance; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

Table 33.1. Causes of Nonalcoholic Fatty Liver Disease

Type of Cause	*Characteristics*
Primary	Obesity, glucose intolerance, type 2 diabetes mellitus, hypertriglyceridemia, low HDL cholesterol, hypertension
Nutritional	Protein-calorie malnutrition, rapid weight loss, gastrointestinal bypass surgery, total parental nutrition
Pharmacologic	Glucocorticoids, estrogens, tamoxifen, amiodarone, methotrexate, diltiazem, zidovudine, valproate, aspirin, tetracycline, cocaine
Metabolic	Lipodystrophy, hypopituitarism, dysbetalipoproteinemia, Weber-Christian disease
Toxic	Poisoning from *Amanita phalloides* (a mushroom), phosphorus, petrochemicals, *Bacillus cereus* toxin
Infectious	Human immunodeficiency virus, hepatitis C, small-bowel diverticulosis with bacterial overgrowth

Abbreviation: HDL, high-density lipoprotein.
Adapted from Angulo P. Nonalcoholic fatty liver disease. In: Talley NJ, Locke GR III, Saito YA, editors. GI epidemiology. Malden (MA): Blackwell Publishing; c2007. p. 247-53. Used with permission.

ultrasonography or computed tomography (CT) (as described below) and often is an incidental finding, prompting further investigation or referrals.

Because a patient with NAFLD or NASH is commonly asymptomatic, fibrosis can progress over many years, and the patient may then present with cirrhosis. NAFLD also should be considered as a possible differential diagnosis in cases of "cryptogenic" cirrhosis. The prevalence of metabolic risk factors such as diabetes mellitus and obesity is similar among patients with cryptogenic cirrhosis and NASH, but less frequent among patients with cirrhosis of other causes, suggesting that NASH accounts for a substantial proportion of cases of cryptogenic cirrhosis. Hepatic steatosis has been observed to disappear over time in patients with NASH-related cirrhosis, potentially masking the diagnosis. Not infrequently, recurrent NASH occurs in patients who received a liver transplant for cryptogenic cirrhosis. Rarely, NASH could be a consideration for patients who have subacute liver failure, because they may have a background of asymptomatic NASH and an unknown stimulus that precipitates liver failure (in an already metabolically stressed liver).

Comorbidities Associated With NAFLD

The comorbidities most commonly associated with NAFLD are the components of metabolic syndrome. The most commonly used definition is from the 2005 recommendations of the National Cholesterol Education Program (Adult Treatment Panel III) (Table 33.3). An associated condition not included in this definition is obstructive sleep apnea. Of patients with NAFLD, 50% to 90% are obese (body mass index [BMI] [calculated as weight in kilograms divided by height in meters squared] ≥30), 55% to 65% have dyslipidemia, and 60% to 70% have hypertension. Type 2 diabetes mellitus is present in 30% to 60% of NAFLD patients, and, if tested, up to 50% of nondiabetic patients may have insulin resistance. Almost 50% of patients with NAFLD have metabolic syndrome (ie, ≥3 features of the syndrome). Also, about 75% of lean patients (BMI <25) with NAFLD have at least 1 feature of metabolic syndrome. In patients with metabolic syndrome, over 80% have steatosis on ultrasonography.

Most patients with NAFLD who have a BMI of 30 or more also meet the criteria for central obesity, as defined by waist circumference (Table 33.3). Fat in an intra-abdominal (visceral) location is metabolically different from fat in a more peripheral or subcutaneous location. The presence and severity of NAFLD correlate more strongly with central obesity than with BMI. Some patients with NAFLD may have a BMI less than 30 and still have central obesity, whereas many persons with a high BMI do not have NAFLD. Body fat distribution differs among ethnic groups, and this may be one of the factors that explains the differences in the prevalence of NAFLD among ethnic groups in the United States. For example, the prevalence is higher among adult Hispanics (45%) than among adult whites (33%) and adult African Americans (24%).

Table 33.2. Principal Clinical, Laboratory, Histologic, and Diagnostic Characteristics of Patients with Nonalcoholic Fatty Liver Disease (NAFLD)

Type of Feature	*Characteristics*
Clinical	Usually asymptomatic; sometimes mild right upper quadrant discomfort, hepatomegaly, acanthosis nigricans, or "cryptogenic" cirrhosis
	Often associated with features of metabolic syndrome: diabetes mellitus, obesity, dyslipidemia (hypertriglyceridemia, low HDL cholesterol, hypobetalipoproteinemia), and cardiovascular disease
Biochemical	Increased AST and ALT levels (usually <5-fold ULRR)
	Increased levels of alkaline phosphatase and γ-glutamyltransferase (usually <3-fold ULRR)
	AST:ALT ratio <1:1
	Hyperinsulinemia and insulin resistance
	Dyslipidemia and increased ferritin level
Histologic	Steatosis (fatty infiltration >5% hepatocytes)
	Necroinflammation (lobular or portal inflammation, Mallory bodies, ballooning)
	Fibrosis (perisinusoidal, perivenular, bridging, cirrhosis)
Imaging	Imaging indicative of fatty infiltration of the liver (ultrasonography, computed tomography, magnetic resonance imaging, magnetic resonance spectroscopy)
Exclusion of other causes (alcohol abuse, secondary causes)	Alcohol intake <140 g weekly for women and <210 g weekly for men
	Absence of liver disease of viral, autoimmune, or genetic origin

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; ULRR, upper limit of the reference range.
Adapted from Moscatiello S, Manini R, Marchesini G. Diabetes and liver disease: an ominous association. Nutr Metab Cardiovasc Dis. 2007 Jan;17(1):63-70. Used with permission.

Table 33.3. National Cholesterol Education Program (Adult Treatment Panel III) Criteria for Metabolic Syndrome

Criterion[a]	*Definition*
Impaired glucose tolerance	Fasting plasma glucose ≥100 mg/dL
Abdominal obesity[b]	Waist circumference >102 cm for men and >88 cm for women
Hypertriglyceridemia	≥150 mg/dL or drug treatment for high triglyceride level
Low levels of HDL	<40 mg/dL in men, <50 mg/dL in women, or drug treatment for low HDL
High blood pressure	≥130/85 mm Hg or drug treatment for hypertension

Abbreviation: HDL, high-density lipoprotein.
[a] Patient must meet 3 or more of these criteria.
[b] The International Diabetes Federation uses the same criteria but defines the waist circumference criteria by ethnicity: South Asian, Chinese, and South or Central American, 90 cm for men and 80 cm for women; Japanese, 85 cm for men and 90 cm for women; and all others, 94 cm for men and 80 cm for women.
Adapted from National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 Dec 17;106(25):3143-421. Used with permission.

BMI can be affected also by volume status in a patient with cirrhosis. Because the calculation relies on weight in kilograms, the presence of ascites and edema must be accounted for clinically. In addition, although waist circumference is a better measure than BMI in noncirrhotic patients, it is of limited value in patients with ascites fluid.

NAFLD is not only intricately tied to metabolic syndrome but also to overt cardiovascular disease (and vice versa). In patients with type 2 diabetes mellitus, up to 70% have ultrasonographic evidence of NAFLD (86% have normal levels of liver enzymes). These patients with NAFLD have higher prevalence rates of cardiovascular disease than diabetic patients without NAFLD. In patients undergoing coronary angiography, with or without diabetes, it has been shown that the ultrasonographically confirmed presence of NAFLD is the strongest predictor of a positive angiogram (even stronger than diabetes or smoking). Patients with carotid artery disease seen on imaging were more likely to have not only increased steatosis but also more necroinflammation and fibrosis, as seen in liver biopsy specimens. NAFLD has been linked with increased cardiovascular disease that is independent of metabolic syndrome in nonobese and in nondiabetic populations as well.

Biochemical Features

Serum liver enzyme abnormalities are generally an increase in the level of ALT or AST (or both). The increase is usually less than 5-fold the upper limit of the reference range. Aminotransferase levels in patients with NAFLD fluctuate; with any 1 measurement, 78% of patients have normal levels, but increased levels are detected in more than 20% of these patients if the measurement is repeated several times during follow-up. Alkaline phosphatase and γ-glutamyltransferase levels may be increased modestly (generally <3-fold the upper limit of the reference range) in one-third of patients; rarely, the level of 1 or both of these enzymes has been reported to be increased without an increase in aminotransferase levels. Hyperbilirubinemia, low albumin levels, or an increase in the international normalized ratio usually indicates advanced liver disease and cirrhosis.

Serum iron test results are commonly abnormal: Ferritin levels are increased in up to 50% of patients and transferrin saturation is increased in up to 10%. These findings potentially may lead to confusion about a diagnosis of hemochromatosis. The presence of heterozygous *HFE* gene mutations does not appear to be associated with hepatic iron loading or liver fibrosis. Testing for antinuclear antibody or anti–smooth muscle antibody (or both) is recommended for screening for autoimmune hepatitis in patients with chronically increased enzyme levels. However, serum autoantibodies are present in 23% to 36% of patients with NAFLD, but the liver biopsy features help to exclude the diagnosis of autoimmune hepatitis in most patients with NAFLD who have a positive test for antinuclear antibody or anti–smooth muscle antibody (or both).

Imaging Features

Ultrasonography, CT, and magnetic resonance imaging (MRI) can be used to noninvasively diagnose fatty infiltration of the liver. Hepatic steatosis causes increased echogenicity on ultrasonography, which can be contrasted with the lower echogenicity of the spleen or renal cortex (Figure 33.1). The use of ultrasonography for detecting hepatic steatosis (≥30% of hepatocytes must be steatotic) has a sensitivity of 80% to 94% and a specificity of 88% to 95%. With morbidly obese patients, the sensitivity decreases to 49% and the specificity decreases to 75%. If detected with ultrasonography, fatty infiltration is highly likely to be present, but if fatty infiltration is not detected with ultrasonography, the diagnosis should not be ruled out.

On noncontrast CT images, hepatic steatosis has a low attenuation and appears darker than the spleen (Figure 33.2). The sensitivity of CT for detecting hepatic steatosis of more than 33% is as high as 93%, with a positive predictive value of 76%. Both phase-contrast MRI techniques and magnetic resonance (MR) spectroscopy are reliable for detecting steatosis and offer good correlation with the volume of liver fat. A liver fat content of more than 5% apparent on MR spectroscopy indicates steatosis. However, the routine application of MRI is limited by cost and lack of availability.

Histologic Features

Histologically, NAFLD is indistinguishable from liver damage that results from alcohol abuse. Liver biopsy features include steatosis, mixed inflammatory cell infiltration, hepatocyte ballooning and necrosis, glycogen nuclei, Mallory hyaline, and fibrosis. The presence of steatosis alone or in combination with the other features accounts for the wide spectrum of NAFLD (Figure 33.3). Steatosis is present predominantly as macrovesicular fat, although some hepatocytes may show an admixture with microvesicular steatosis. Fatty infiltration that is mild is concentrated typically in acinar zone 3; moderate to severe fatty infiltration shows a more diffuse distribution. The inflammatory

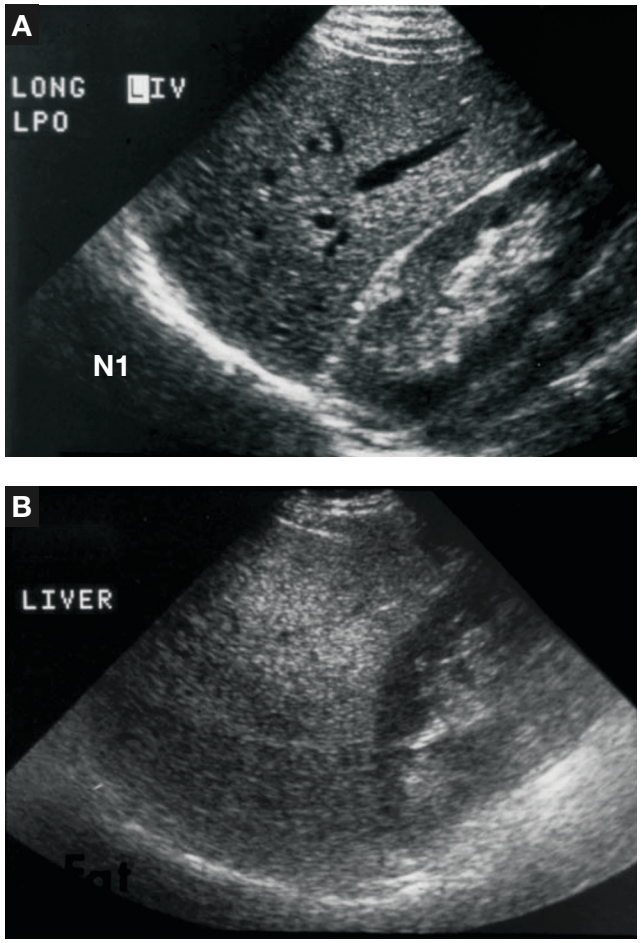

Figure 33.1. Ultrasonic Findings in Hepatic Steatosis. A, Normal liver has distinctive vascular features. B, Liver with fatty infiltration has a diffuse bright echotexture and blurring of hepatic vessels.

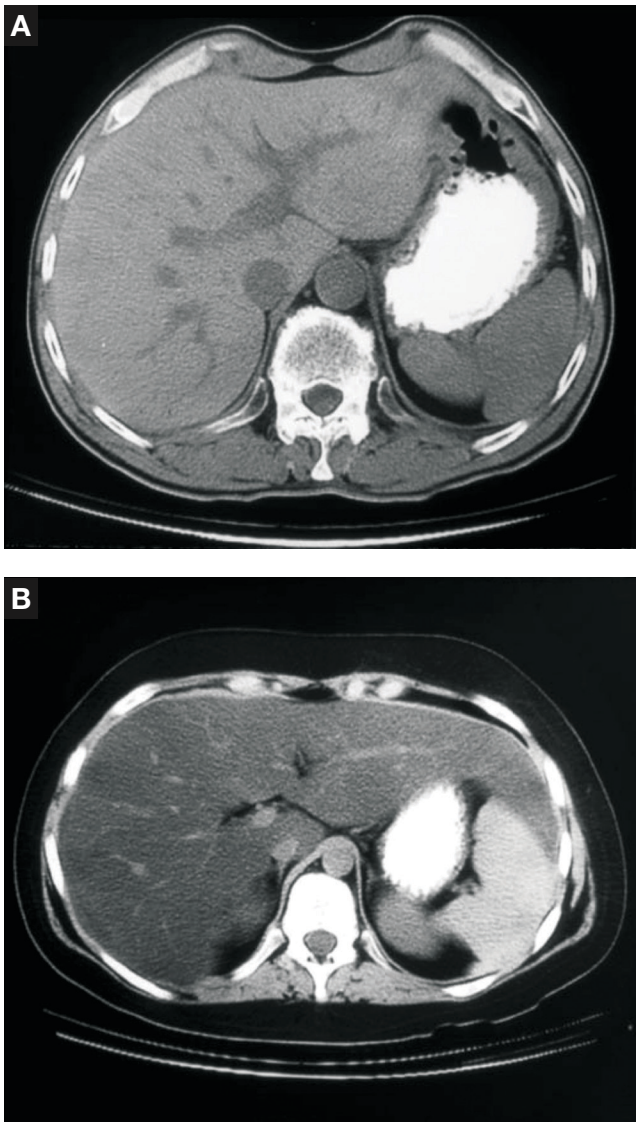

Figure 33.2. Features of Hepatic Steatosis Visualized With Computed Tomography. A, Normal liver has no attenuation of the signal compared with the spleen. B, Liver with fatty infiltration has an attenuated signal compared with the spleen.

infiltrate usually consists of mixed neutrophils and lymphocytes and predominates in zone 3.

Ballooning degeneration of hepatocytes results from the intracellular accumulation of fluid and is characterized by swollen cells typically noted in zone 3 near the steatotic hepatocytes. Mallory hyaline is found in about one-half of adult patients who have NAFLD and usually is located in ballooned hepatocytes in zone 3, but it is neither unique nor specific for NAFLD. The pattern of fibrosis is a characteristic feature of NAFLD. Collagen is laid down first in the pericellular space around the central vein and in the perisinusoidal region in zone 3. In some areas, the collagen fibers invest single cells in a pattern referred to as "chicken-wire fibrosis," as described in alcohol-induced liver damage. This pattern of fibrosis helps to distinguish NAFLD and alcoholic liver disease from other forms of liver disease in which fibrosis shows an initial portal distribution (Figure 33.3).

Portal tracts are relatively spared from inflammation, although children with NAFLD may show a predominance of portal-based injury instead of a lobular pericentral injury. Mallory hyaline is notably sparse or absent in children with NAFLD. In some patients with cirrhotic-stage NAFLD, the features of steatosis and necroinflammatory activity may no longer be present. Although liver biopsy is the gold standard for diagnosing NASH and staging fibrosis, sampling variability may underestimate the severity of liver injury in up to 30% of patients.

Diagnosis

The gold standard for diagnosing NAFLD is clinicopathologic correlation, based on the confirmation of steatosis by liver biopsy and appropriate exclusion of other causes (Table 33.2). It is important to exclude alcohol abuse as the cause of fatty liver. It is known that a minimal amount of alcohol—20 g daily (1-2 standard drinks) for women and 30 g daily (2-3 standard drinks) for men—can induce fatty liver, and these limits are commonly used to distinguish between alcoholic and nonalcoholic fatty liver. Secondary causes of NAFLD (Table 33.1) should be excluded because NAFLD associated with these conditions has a different course and treatment.

For patients with persistently increased serum levels of liver enzymes, other causes of NAFLD and other common causes of liver disease should be excluded by clinical review and laboratory testing. With the increasing prevalence of NAFLD, more patients may have a second cause of liver disease superimposed on a background of steatosis. Thus, it is essential to exclude viral

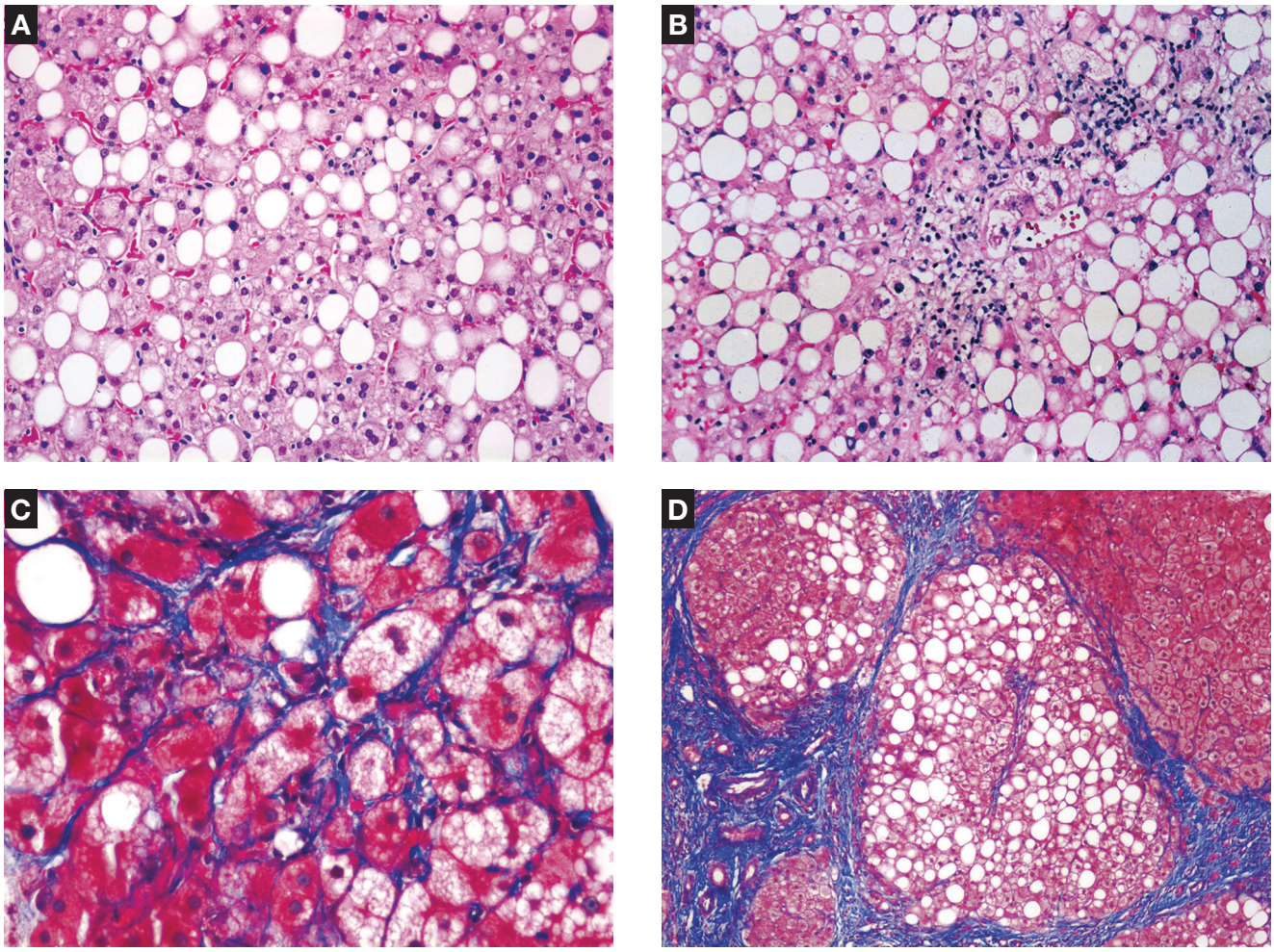

Figure 33.3. Liver Biopsy Specimens. A, Bland steatosis. Steatosis is present predominantly as macrovesicular fat, although some hepatocytes may show an admixture with microvesicular steatosis (hematoxylin-eosin, original magnification ×100). B, Nonalcoholic steatohepatitis with steatosis, inflammatory infiltrate, Mallory hyaline, and hepatocyte ballooning (hematoxylin-eosin, original magnification ×100). C, Pericellular and perisinusoidal fibrosis in zone 3 (Masson trichrome, original magnification ×400.) D, Cirrhotic stage of nonalcoholic fatty liver disease (Masson trichrome, original magnification ×100).

hepatitis, drug-induced liver disease, celiac disease, autoimmune disease, vascular disease, and metabolic diseases such as alpha$_1$-antitrypsin deficiency. In a young person, Wilson disease can manifest with steatohepatitis findings on biopsy, requiring hepatic copper quantification, slit-lamp examination, and 24-hour urine studies to rule it out. Determining the need for a liver biopsy to establish the diagnosis of NAFLD should be individualized. Liver biopsy may be useful for diagnosing NAFLD when a potential differential diagnosis is suggested by clinical, serologic, or biochemical testing. These situations include the presence of autoantibodies or increased iron indices, a history of recent medication change, or the absence of detectable hepatic steatosis on cross-sectional imaging. Also, the persistence of increased levels of aminotransferases after 3 to 6 months of lifestyle intervention with appropriate weight loss and control of lipid and glucose levels may suggest another diagnosis and dictate the need for liver biopsy.

Staging

Liver biopsy is the only investigation that can differentiate NASH from simple steatosis as well as stage the extent of fibrosis. Standard imaging studies such as ultrasonography, CT, and MRI cannot distinguish between steatosis and NASH, nor can they stage the degree of hepatic fibrosis. Recently, measuring liver stiffness with ultrasound- or MR-based elastography has been proposed as potentially useful for quantifying liver fibrosis in patients with a wide range of chronic liver disease; however, further evaluation of these techniques is needed in patients with NAFLD. Obesity and abdominal wall thickness can limit the effectiveness of ultrasound-based elastography because the depth of penetration is limited, but thus far, they do not seem to have a major effect on MR-based elastography.

The potential benefits of liver biopsy must be weighed against the small risk of complications, including pain, bleeding, and, rarely, death. Several clinical and laboratory features are recognized in association with NASH or advanced fibrosis (or both) in patients with NAFLD, including older age, presence of diabetes, higher BMI, higher AST:ALT ratio, and low albumin level and platelet count.

Advanced fibrosis in patients with NAFLD has been associated with levels of serum markers of fibrogenesis, including hyaluronic acid, propeptide of type III collagen, and tissue inhibitor of matrix metalloproteinase 1. These serum markers have been

combined in the Enhanced Liver Fibrosis score, which is a numerical value that is used to predict the presence and severity of liver fibrosis in NAFLD. Similarly, the FibroTest (BioPredictive; FibroSURE in the United States [LabCorp]), which has been studied extensively in viral hepatitis to predict the severity of fibrosis, has been evaluated in NAFLD. A combination of several other markers is used in the SteatoTest (BioPredictive). In addition, caspase-3–generated cytokeratin-18 fragments, a marker of apoptosis measured in plasma, has shown good promise for distinguishing between simple steatosis and NASH. Multiple other noninvasive test results have been studied, but overall, additional validation is required before the markers can be used routinely in clinical practice. (For a summary of these tests, see the article by Festi et al in the Suggested Reading list.)

Prognosis

Knowledge of the histologic subtype of NAFLD and the stage of fibrosis is useful in determining prognosis and may alter clinical management. The natural history of uncomplicated hepatic steatosis is relatively benign; follow-up of 342 patients for over 15 years showed progression to cirrhosis and liver-related mortality in less than 1% of patients. In contrast, NASH may progress to cirrhosis in up to 11% of patients, and about 7% of NASH patients die of liver-related complications within 15 years after diagnosis. Therefore, the diagnosis of NASH, particularly when associated with any fibrosis, may prompt a more aggressive therapeutic approach toward metabolic risk factors and participation of patients in clinical trials with novel agents, if available. The presence of advanced fibrosis or cirrhosis should initiate screening for hepatocellular carcinoma and esophageal varices, with closer monitoring for disease-related complications.

Prevention

No studies have been aimed at preventing the development of NAFLD. Achieving and maintaining appropriate weight control would be expected to prevent the development of metabolic syndrome, and thus NAFLD, in many people. The treatment of established glucose and lipid abnormalities may reduce the likelihood of NAFLD or NASH, but no data exist that specifically validate this. However, data from the Diabetes Prevention Program in the United States showed that both lifestyle intervention and the insulin-sensitizing drug metformin significantly decreased the development of metabolic syndrome, which, intuitively, may prevent the development of NAFLD.

Treatment

Weight Loss

Weight loss, particularly if gradual, may lead to improvement in the histologic features of the liver in NAFLD. However, the rate and degree of weight loss required for normalization of the histologic features have not been established clearly. Rapid weight loss or very low calorie diets may cause worsening of the histologic features and, thus, should be avoided. Weight loss of as little as 5% of the baseline weight has been shown to improve or normalize ALT levels in NASH, and a 7% to 10% weight reduction produced histologic improvement. Studies have shown that a rigorous lifestyle modification program is necessary for patients to achieve successful weight loss. These modifications include the following: 1) dietary restrictions, depending on the baseline weight (1,000-1,200 kcal daily if the baseline weight is <91 kg, or 1,200-1,500 kcal daily if the baseline weight is >91 kg), and a daily fat gram goal of 25% of caloric requirements. 2) Physical activity (goal of 10,000 steps daily and 200 minutes weekly of moderate-intensity activity). 3) Weekly group sessions for behavioral modifications. With rigorous programs, which usually are accomplished through the work of a multidisciplinary team, successful weight loss and histologic improvement are possible.

Weight loss agents such as orlistat and sibutramine produce only modest weight loss (generally 3-5 kg more than placebo) at the expense of adverse effects: Orlistat can cause diarrhea, gastrointestinal pain, and vitamin deficiencies, and sibutramine can cause hypertension and drug interactions. Rimonabant (a cannabinoid type-1 receptor antagonist) produced clinically meaningful weight loss and improvement in metabolic syndrome measures, but it has been withdrawn from the market because of its psychiatric side effects. Newer agents recently approved by the US Food and Drug Administration for weight loss (phentermine-topiramate and lorcaserin) have not been studied in NAFLD.

Bariatric surgery has become one of the most common surgical procedures performed in the United States. Several surgical procedures are available to reduce the gastric reservoir (restrictive procedures) and to reduce intestinal absorption of nutrients (malabsorptive procedures). Because weight loss after these procedures can be extreme and rapid, careful monitoring is required. Several studies have shown improvement in metabolic syndrome measures and improvement in or resolution of steatosis. The severity of inflammation and fibrosis seen in liver biopsy specimens often improves 5 years after bariatric surgery, but both inflammation and fibrosis worsen in some patients. For medically complicated obesity, bariatric surgery should be considered.

Nonpharmacologic Treatment

Caffeine from regular coffee (not espresso) has been associated with reduced fibrosis progression in patients with established NASH. Two studies confirmed that more than 2 cups of coffee daily potentially affected disease progression favorably. Further studies will be performed.

Results from the use of probiotics with or without prebiotics also look favorable in 3 very small randomized studies to date. Thus far, their use has been associated with reduced liver enzyme abnormalities, but histologic effects are not known. Studies are ongoing in the area.

Pharmacologic Treatment

Because achieving and maintaining appropriate weight control is difficult for most obese patients, the use of medications to directly reduce the severity of liver damage independently of weight loss is an attractive alternative. Medical management of metabolic syndrome is important, but pharmacologic therapy also may benefit patients who do not have metabolic syndrome (Box 33.1). Until recently, the results of only pilot studies suggested that insulin-sensitizer medications, antioxidants, lipid-lowering medications, and some hepatoprotective medications may be of potential benefit. Most of these studies were uncontrolled, open-label studies that lasted 1 year or less, and only a few evaluated the effect of treatment on the histologic features of the liver. More data are available now for oral hypoglycemics, vitamin E, and betaine, and they validate the findings of some of the pilot studies.

A collaboration of investigators, the NASH Clinical Research Network, has demonstrated histologic benefit with vitamin E

Box 33.1. Therapeutic Interventions for Nonalcoholic Fatty Liver Disease

Sufficient evidence of benefit

- Weight loss of 7%-10% of body weight
  - Nonsurgical—caloric restriction, 10,000 steps daily, and 200 minutes weekly of moderate-intensity exercise
  - Surgical—bariatric surgery
- Vitamin E

Insufficient evidence but possible benefit

- Pioglitazone
- Rosiglitazone
- Metformin
- Statins
- Fish oil
- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor blockers
- Pentoxifylline
- Coffee (regular, not espresso)
- Probiotics with or without prebiotics

No benefit

- Ursodiol
- Betaine

therapy (800 international units daily) or pioglitazone therapy (30 mg once daily) over placebo for nondiabetic patients who have NASH. This study, with approximately 80 patients in each treatment group followed for more than 2 years, showed improvement in the serum levels of aminotransferases and biopsy evidence of improved steatosis and inflammation scores in both treatment groups compared with placebo. Improvement was more statistically significant in the vitamin E group. However, fibrosis scores did not improve in any treatment group. Although improvement in aminotransferase levels and biopsy findings was greater in the treatment groups, only 36% to 47% of the patients had histologic resolution of definite NASH. More importantly, 30% of patients in the placebo group had elements of histologic improvement and 21% had histologic resolution of definite NASH, as seen in biopsy specimens. The beneficial effects of vitamin E and pioglitazone in NASH should be weighed against the risk of serious adverse events, such as increased mortality or increased prostate cancer associated with vitamin E at a dose of 400 international units daily or higher and severe heart failure associated with pioglitazone.

Administration of rosiglitazone for 12 months led to modest improvement in steatosis and ALT levels, compared with placebo, but extending treatment for 2 more years was not associated with additional laboratory or histologic benefit. Both pioglitazone and rosiglitazone induce notable weight gain in patients receiving these medications, without subsequent weight loss when this medical therapy is stopped. This concern, in combination with the adverse events described above, mandates close examination of the risk to benefit ratio for individual patients. Thus, the role of vitamin E and glitazones in treating NASH is unclear. Certainly, if a patient has underlying diabetes, oral hypoglycemic agents (including metformin or other agents) would be appropriate first-line agents for controlling diabetes.

Betaine, an antioxidant (methyl donor for the remethylation of homocysteine), was thought to be antisteatotic and antiinflammatory (in animal studies) and of possible benefit for the treatment of NASH (in a pilot study with humans). However, a large randomized controlled trial found no histologic benefit for humans with NASH. In pilot studies of NASH patients, ursodiol was thought to improve serum biochemistry measures, but a larger, randomized, placebo-controlled study established that this agent had no histologic benefit compared with placebo after 2 years of treatment. A randomized placebo-controlled trial from Switzerland confirmed these findings, but this trial also included a group receiving the combination of ursodiol and vitamin E; a modest histologic benefit (for steatosis only) was reported. Pilot studies involving agents such as pentoxifylline and probucol have indicated that these agents may have benefit (and adverse effects), but further validation is required.

Initial studies with statins suggested a possible decrease in the serum levels of aminotransferases, but a recent, small randomized controlled trial of only 12 months' duration did not confirm histologic benefit. Fish oil has antiinflammatory effects and is an effective agent for decreasing triglyceride levels. In animal studies of NASH, fish oil (which contains omega-3 fatty acids) has been associated with improved steatosis and inflammation, and human studies have demonstrated biochemical improvement and radiologic improvements in steatosis but have not had adequate histologic assessment. Fish oil is safe and well tolerated; thus, if hypertriglyceridemia is present, fish oil may be the agent to select first. Further study is ongoing to determine its direct effect on liver histology. According to the American Heart Association guidelines, if a patient has hypercholesterolemia, statins and other agents are warranted to control hyperlipidemia. These agents are safely used in patients with chronic liver disease, including NAFLD and NASH.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown in animal studies to be antifibrogenic and may affect insulin resistance. Studies of hepatitis C patients who have hypertension have shown benefit in the reduction of fibrosis when patients received therapy with ACEIs and ARBs compared with other antihypertensive agents. Thus far, studies of NASH have shown that ACEIs and ARBs improve serum biochemistry measures, insulin resistance, and blood pressure. One study showed a reduction in adipose tissue as well. In this study, steatosis was reduced with losartan and was further reduced with the addition of statin medication. If a patient with NASH is hypertensive and has normal renal function and potassium levels, treatment with ACEI or ARB agents would be an appropriate consideration.

A meta-analysis of all NASH placebo-controlled trials has reported that up to 30% of placebo patients may have modest histologic improvement. Previously, it was determined that up to 20% to 30% of liver biopsy specimens may be understaged by sampling error. Thus, it cannot be overstated that NASH studies need to be placebo-controlled to truly assess the benefit of any agent studied.

For patients with cirrhotic-stage NAFLD and decompensated disease, liver transplant is a potentially life-extending therapeutic alternative. However, some patients with cirrhotic-stage NAFLD have comorbid conditions that often may limit their candidacy for liver transplant.

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34

Liver Disease and Pregnancy[a]

J. EILEEN HAY, MB, ChB

Because most pregnant women are young and healthy, liver disease is uncommon in this patient population. Also, the presence of liver disease must not be confused with some of the physiologic changes of pregnancy that mimic features commonly associated with liver dysfunction (Table 34.1), including spider nevi and palmar erythema in 50% of pregnant women, increased serum level of alkaline phosphatase from placental production, and decreased serum level of hemoglobin with expanded blood volume. Increased levels of bilirubin and transaminases, hepatomegaly, splenomegaly, liver tenderness, and bruits do not occur in normal pregnancy, and the clinical finding of jaundice is always abnormal. Abnormal liver enzyme levels occur in 3% to 5% of pregnancies and jaundice occurs in 0.1%, with a clinical significance that is highly variable, from self-limiting to rapidly fatal.

For diagnostic purposes, it is useful to divide liver diseases in pregnant women into 3 main categories (Table 34.2):

1. Liver diseases occurring coincidentally in a pregnant woman (viral hepatitis is the most common cause of jaundice in pregnant patients)
2. Pregnancy occurring in a woman with chronic liver disease
3. Liver diseases unique to pregnancy, including hyperemesis gravidarum, intrahepatic cholestasis of pregnancy (ICP), preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, and acute fatty liver of pregnancy (AFLP)

The liver diseases unique to pregnancy can be considered liver complications of pregnancy itself, and they have a characteristic timing in relation to the trimesters of pregnancy. Hepatitis E and herpes hepatitis, although not related etiologically to pregnancy, characteristically produce a fulminant and often deadly disease in the third trimester of pregnancy. Recent data suggest that most liver disease in pregnancy is pregnancy-related, especially severe liver disease in the third trimester, and incidental and chronic liver diseases are uncommon.

Diagnostic Strategy With Pregnant Patients

Optimal management of pregnant patients who have abnormal liver test results or jaundice requires accurate and often rapid diagnosis. The clinical presentation and trimester of pregnancy are diagnostically important (Table 34.2). Answers to the following questions help formulate a rational approach to these patients:

1. Are there any features of underlying chronic liver disease (including liver transplant) or risk factors for viral disease?
2. Is the presentation compatible with acute viral hepatitis?
3. Are there any features to suggest biliary disease?
4. Is there any history of drugs or toxins?
5. Are there any features of Budd-Chiari syndrome?
6. Is there any evidence of sepsis or risk factors for sepsis?
7. Does the presentation fit one of the liver diseases unique to pregnancy?

Clinical features and laboratory testing allow a diagnosis for most patients, but for some patients, imaging of the liver, endoscopic retrograde cholangiopancreatography (ERCP), or liver

[a] Portions of this chapter were adapted from Hay JE. Liver disease in pregnancy. Hepatology. 2008 Mar;47(3):1067-76; and Hay JE. Liver disease, pregnancy and. In: Johnson LR, editor. Encyclopedia of gastroenterology. Vol 2. Amsterdam: Elsevier Academic Press; c2004. p. 533-8. Used with permission.

Abbreviations: AFLP, acute fatty liver of pregnancy; ERCP, endoscopic retrograde cholangiopancreatography; HELLP, hemolysis, elevated liver enzymes, and low platelet count; ICP, intrahepatic cholestasis of pregnancy; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; UDCA, ursodeoxycholic acid

Table 34.1. Physiologic Changes in Liver Test Results During Pregnancy

Test	*Change*
Bilirubin	Unchanged
AST, ALT	Unchanged
Prothrombin time	Unchanged
Alkaline prosphatase	Increased 2- to 4-fold
Fibrinogen	Increased 50%
Globulins	
α-Globulin	Increased
β-Globulin	Increased
γ-Globulin	Decreased
Alpha fetoprotein	Increased moderately, especially with twins
Leukocytes	Increased
Ceruloplasmin	Increased
Cholesterol	Increased 2-fold
Triglycerides	Increased

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 34.2. Causes and Timing of Liver Disease During Pregnancy

Disease Category	*Specific Disease*	*Trimester of Pregnancy*
Chronic liver disease or portal hypertension	Chronic hepatitis B	1-3
	Hepatitis C	1-3
	Autoimmune disease	1-3
	Wilson disease	1-3
	Cirrhosis from any cause	1-3
	Extrahepatic portal hypertension	1-3
Liver disease coincidental with pregnancy	Acute viral hepatitis	1-3
	Budd-Chiari syndrome	Postpartum
	Gallstones	1-3
	Drug-induced	1-3
Liver disease unique to pregnancy	Intrahepatic cholestasis of pregnancy	2 or 3
	Hyperemesis gravidarum	1
	Preeclampsia	3, late 2
	HELLP syndrome	3, late 2
	Acute fatty liver of pregnancy	3

Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelet count.

biopsy is necessary. Ultrasonography of the liver and abdomen is safe during all 3 trimesters of pregnancy and is helpful in the evaluation of biliary tract disease, patency of hepatic and portal veins, AFLP, hematomas, and rupture. To confirm the diagnosis of choledocholithiasis, ERCP can be performed safely in pregnant women. Radiation exposure with fluoroscopy is well below the fetal safety level. Midazolam, meperidine, and glucagon can be given safely. If indicated, sphincterotomy and stone extraction should be performed at the same time. Hepatic venography or magnetic resonance imaging is necessary to confirm the diagnosis of Budd-Chiari syndrome in patients who have clinical and ultrasonographic features compatible with the syndrome.

Liver Diseases Occurring Coincidentally in Pregnant Patients

Viral Hepatitis

Jaundice in pregnancy may be due to any of the many causes of jaundice in nonpregnant patients. Viral hepatitis (due to hepatitis A, B, C, D, or E virus; cytomegalovirus; or Epstein-Barr virus) accounts for 40% of cases of jaundice in pregnant women in the United States. Hepatitis A, B, and C have the same frequency in pregnant and nonpregnant populations and during each trimester of pregnancy. Acute hepatitis A occurs in 1 per 1,000 pregnant women and acute hepatitis B in 2 per 1,000; hepatitis D is rare. Hepatitis E is rare in the United States but is endemic in large areas of Asia, Africa, and Central America, where, in the third trimester of pregnancy, it becomes fulminant, with a high mortality rate that probably is influenced by malnutrition. In India, 25% of women with acute liver failure are pregnant, and in almost all of them, liver failure is due to acute viral hepatitis. Herpes simplex hepatitis is rare.

Apart from herpes simplex, the clinical and serologic course of acute hepatitis in pregnant women is the same as in nonpregnant patients, and hepatitis does not appear to adversely affect the pregnant state. Even though herpes simplex hepatitis is rare, it must be diagnosed because specific therapy is lifesaving. In pregnant women, it typically occurs as a primary infection in the third trimester and has systemic features with a prodrome and fever, diffuse vesicular rash and leukopenia, vulvar or oropharyngeal vesicular lesions, and coagulopathy. These patients usually are anicteric even with liver failure.

Serologic testing for hepatitis A, B, and C viruses; Epstein-Barr virus; and cytomegalovirus should be performed in all cases of acute jaundice in pregnancy. Antibody to hepatitis E virus should be assayed if the patient is from, or has been a recent traveler to, an area where hepatitis E is endemic. Testing for hepatitis C virus RNA in the absence of antibody to hepatitis C virus has been positive in several pregnant patients who subsequently developed hepatitis C. Serologic testing, liver biopsy, and culture may be necessary to diagnose herpes simplex hepatitis.

Management of patients who have acute viral hepatitis is supportive except for herpes simplex infection, for which prompt therapy with acyclovir or vidarabine is lifesaving and without which 50% of mothers die of the disease. Acute or chronic viral hepatitis is not an indication for the termination of pregnancy, except in the case of a herpes infection that does not respond to antiviral therapy. Congenital fetal malformations occur only with early cytomegalovirus infection. Viral hepatitis is not an indication for cesarean delivery, and breastfeeding should not be discouraged.

For patients with chronic hepatitis B who receive antiviral therapy, this therapy should be replaced with agents that are safe to use in pregnancy (eg, lamivudine and tenofovir). Interferon therapy is contraindicated in pregnancy.

Perinatal transmission of hepatitis B is highest in mothers with acute hepatitis, especially in those who test positive for hepatitis B e antigen in the third trimester (50%-80%); lower in mothers with hepatitis B e antibodies (25%); and lowest in carriers (5%). From 80% to 90% of these mothers' babies become chronic carriers. Transmission of hepatitis B is not transplacental but occurs at delivery and is preventable in more than 95% of cases by passive-active immunoprophylaxis of the babies at birth (Table 34.3). Babies at risk for vertical transmission despite immunoprophylaxis are those whose mothers have high levels of viremia (>8 $\log_{10}$ IU/mL). Treatment with lamivudine in the last weeks of pregnancy can reduce transmission risk and appears to be safe. Breastfeeding is not contraindicated even if the mother has active hepatitis B. Vertical transmission of hepatitis A and D is rare. The frequency of mother-to-infant transmission of hepatitis C is 1% to 5%, with maternal risk factors being coinfection with human immunodeficiency virus, history of intravenous drug abuse, and maternal viremia of more than 10^6 copies/mL. Transmission is not affected by mode of delivery or breastfeeding. Newborns of mothers with hepatitis A in the third trimester

Table 34.3. Prophylaxis Regimen for Babies of HBsAg-Positive Mothers

Preparation	*Dose*	*Age at Intramuscular Administration*
HBIG	0.5 mL	Birth
HBV vaccine (recombinant)	0.5 mL (10 mcg)	Birth (2 d) 1 mo 6 mo

Abbreviations: HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

should be given passive immunoprophylaxis with immune globulin within 48 hours after birth. The benefits of immune globulin for babies of mothers seropositive for hepatitis C virus are unknown, and there is no effective therapy for preventing transmission of hepatitis C.

Gallstones and Biliary Disease

Increased lithogenicity of bile and biliary stasis during pregnancy predisposes pregnant women to enhanced formation of biliary sludge and stones. Despite their prevalence, symptomatic gallstones occur in only 0.1% to 0.3% of pregnancies, and symptoms usually develop after multiple pregnancies rather than during gestation. The common clinical presentations are biliary colic (5% of cases of jaundice in pregnancy), gallstone pancreatitis (50% of women younger than 30 years with pancreatitis are pregnant), and, the least common of these, acute cholecystitis. The clinical features of biliary disease and pancreatitis are the same as in nonpregnant patients. The diseases can occur at any time during gestation, and they may recur during pregnancy.

Intractable biliary colic, severe acute cholecystitis not responding to conservative measures, and acute gallstone pancreatitis are indications for immediate cholecystectomy despite the patient's pregnant state. For acute biliary colic or acute cholecystitis, conservative therapy (bed rest, intravenous fluids, and antibiotics) is instituted initially and is successful in more than 80% of patients, with no fetal or maternal mortality. However, because symptoms recur during pregnancy in 50% of patients, cholecystectomy is indicated for all patients with symptoms in the second trimester. For these patients, the operation has very little morbidity or mortality. Indeed, patients who undergo cholecystectomy have better pregnancy outcomes than those treated medically. Surgery is avoided in the first 10 weeks of pregnancy because of the risk of abortion with anesthesia and the potential teratogenic effect of carbon dioxide. In the third trimester, the uterus may impinge into the surgical field; there also is an increased risk of premature labor. Laparoscopic cholecystectomy with added precaution for the pregnant state is now the standard of care for these patients. An impacted common bile duct stone and worsening gallstone pancreatitis are indications to proceed to ERCP, sphincterotomy, and stone extraction under antibiotic coverage.

Other Diseases

Budd-Chiari syndrome is rare and when it occurs in pregnancy, it is usually in the postpartum period. It has been associated with antiphospholipid syndrome, thrombotic thrombocytopenic purpura, preeclampsia, and septic abortion. Sepsis associated with pyelonephritis or abortion can cause jaundice in early pregnancy. Severe gram-negative sepsis with jaundice has been described in the third trimester.

Pregnant Patients With Chronic Liver Disease

Many women with chronic viral or autoimmune hepatitis or Wilson disease are of childbearing age. Chronic hepatitis B is present in 0.5% to 1.5% of pregnancies, and chronic hepatitis C is present in 2.3% of pregnancies in some indigent populations. An uncomplicated pregnancy with no disease flare is expected in patients with mild disease or disease in remission. In women with hepatitis C, transaminase levels may actually decrease and hepatitis C viral RNA levels increase during pregnancy, with the reverse occurring in the postpartum period. Patients with Dubin-Johnson syndrome or benign recurrent intrahepatic cholestasis may become more jaundiced during pregnancy, especially in the second and third trimesters, but the only significance of such jaundice is the necessity to rule out other possible causes. Also, symptomatic therapy for pruritus should be provided. Gilbert syndrome and Rotor syndrome are unaffected by pregnancy.

Autoimmune disease is not expected to flare in pregnancy but is treated with increased doses of corticosteroids as necessary; azathioprine therapy in pregnancy has not been associated with increased fetal risk. Patients with Wilson disease must be treated adequately before pregnancy and continue receiving therapy throughout pregnancy. Discontinuation of therapy poses the risk of fulminant Wilson disease. The best treatment is D-penicillamine, but, rarely, it has been associated with congenital defects; trientine is a safe alternative for fetal health but of less proven efficacy for the mother.

Most patients with advanced cirrhosis are amenorrheic and infertile because of hypothalamopituitary dysfunction, but if pregnancy occurs, maternal and fetal problems can be expected to increase. Little is known about the optimal management of pregnant patients with cirrhosis and portal hypertension in the modern era of obstetrics. The main risk to the mother is massive gastrointestinal tract bleeding (20%-25% of cases), and women with known esophageal varices should be considered for endoscopic therapy, shunt surgery, or even liver transplant before pregnancy. Also, all patients, even if they do not have varices before pregnancy, should undergo upper endoscopy in the second trimester for assessment of varices. If large varices are present, β-blocker therapy is initiated. Whether prophylactic endoscopic therapy for esophageal varices in early pregnancy is beneficial has not been tested. Acute variceal bleeding is managed endoscopically in the same way as for nonpregnant patients, although vasopressin is contraindicated. Little is known about the use of octreotide in pregnancy. Ascites and hepatic encephalopathy are treated in the standard way.

Vaginal deliveries with an assisted, short second stage are preferable because abdominal surgery is avoided. However, for patients known to have large varices, cesarean delivery is recommended to avoid labor and, thus, prevent an increase in portal pressure and the risk of variceal bleeding. Postpartum hemorrhage and bacterial infections are reduced by correction of coagulopathy and antibiotic prophylaxis.

A pregnant liver transplant recipient represents a unique clinical situation requiring specialized care. With the success of liver transplant, more pregnancies are being reported in liver recipients, and a carefully planned pregnancy in a stable, healthy patient beyond the first 2 years after orthotopic liver transplant can have excellent outcomes for the fetus, mother, and graft. However, this is still a high-risk pregnancy, with increased fetal prematurity and dysmaturity. Also, there is some risk to the allograft from acute cellular rejection or recurrent viral hepatitis. Consequently, it is imperative to monitor immunosuppression closely and to adjust

the calcineurin inhibitor doses as needed for the increased blood volume in the second half of pregnancy. Liver function must be monitored regularly, and all liver abnormalities, especially acute cellular rejection, must be investigated and treated as aggressively as in nonpregnant patients.

Liver Diseases Unique to Pregnancy

Liver diseases unique to pregnancy have characteristic clinical features and timing of onset in relation to pregnancy (Table 34.2). Although still poorly understood, some interesting advances have been made recently in understanding these pregnancy-associated diseases. The diseases belong to 1 of 2 main categories depending on whether they are associated with preeclampsia. ICP and hyperemesis gravidarum are not associated with preeclampsia. The preeclampsia-associated liver diseases are preeclampsia itself, HELLP syndrome, and AFLP.

Hyperemesis Gravidarum

Hyperemesis gravidarum is intractable nausea and vomiting in the first trimester of pregnancy and is so severe that intravenous hydration is required. It occurs in 0.3% of pregnancies. Immunologic, hormonal, and psychologic factors associated with pregnancy may have an etiologic role. Risk factors include hyperthyroidism, psychiatric illness, molar pregnancy, preexisting diabetes mellitus, and multiple pregnancies.

Clinical Features and Diagnosis

Vomiting must be severe and intractable to support the diagnosis of hyperemesis gravidarum. It occurs in the first trimester of pregnancy, typically between 4 and 10 weeks of gestation, and may be complicated by liver dysfunction and, occasionally, jaundice. High transaminase levels, up to 20-fold above the reference range, occur in 50% of patients. The diagnosis is made on clinical grounds and rests on the presence of intractable, dehydrating vomiting in the first trimester. Uncomplicated vomiting in pregnancy does not cause liver dysfunction. When transaminase levels are high, serologic testing for viral hepatitis should be performed. In the rare patient who requires liver biopsy to exclude more serious disease, the histologic appearance of the liver is generally normal but may show cholestasis with rare cell dropout. Despite high transaminase levels, no inflammation or notable necrosis is observed.

Management

Hospitalization is necessary for hydration and parenteral nutrition; otherwise, therapy is symptomatic with antiemetics.

Intrahepatic Cholestasis of Pregnancy

ICP is a specific liver disease unique to pregnancy; it is characterized by severe pruritus, mild jaundice, and biochemical cholestasis that appear in the second half of pregnancy and disappear after delivery. These features typically recur in subsequent pregnancies. ICP is second only to viral hepatitis as a cause of jaundice in pregnant women.

Incidence and Cause

ICP is identified all over the world but has striking geographic, ethnic, temporal, and seasonal variations. In the United States, it occurs in 0.1% of pregnancies, with jaundice in 20% of cases, but it has a much higher incidence in some other countries. Recent advances have been made in understanding its cause, which seems to be influenced by genetic, hormonal, and exogenous factors, perhaps of differing importance in different women.

Familial cases and the high incidence in certain ethnic groups (Araucanian Indians of Chile) have long suggested a genetic predisposition to ICP. Pedigree analysis of family members of a child with progressive familial intrahepatic cholestasis has identified a mutation in the MDR3 (*ABCB4*) gene associated with ICP. MDR3 is the transporter for phospholipids across the canalicular membrane. The association of ICP with mutations affecting MDR3 has been confirmed by several investigators, and those mutations may account for 15% of cases of ICP. Gene mutations affecting the canalicular transporters FIC1 and BSEP have also been associated with ICP.

The pathogenesis clearly is related in some way to female sex hormones, as evidenced by the temporal relationship to hormone levels in late pregnancy, the increase in twin pregnancies, and the fact that estrogens may cause cholestasis in nonpregnant women who develop ICP in pregnancy. These and other observations suggest that ICP is due to a genetically abnormal or exaggerated metabolic response by the liver to the physiologic increase in estrogens during pregnancy. Impaired sulfation (an important detoxification pathway) has been identified in some patients with ICP. Abnormalities in progesterone metabolism also have been seen, some probably genetic, some exogenous. Exogenous progesterone therapy administered in the third trimester of pregnancy increases the serum levels of bile acid and alanine aminotransferase, and progesterone given to prevent premature delivery can precipitate ICP in some women. The role of exogenous factors in ICP is suggested by the fact that it recurs in only 45% to 70% of pregnancies and with variable intensity. Also, the clear seasonal variability of ICP suggests modification of the disease by exogenous factors. Dietary factors such as selenium deficiency have been implicated in some studies from Chile.

Fetal complications in ICP are placental insufficiency, premature labor, and sudden fetal death. The pathogenesis of these complications may be due to increased fetal levels of bile acid. Normally, fetal bile acid is transported across the placental membrane to the maternal circulation, and high levels are damaging to the fetus. Abnormal placental transport of bile acid from the fetal circulation to the maternal circulation, increased maternal levels of bile acid, and immaturity of fetal transport systems may all contribute to increased fetal levels of bile acid in ICP.

Clinical Features and Diagnosis

The onset of pruritus at about 25 to 32 weeks of gestation in a patient with no other signs of liver disease is strongly suggestive of ICP. This is especially true if the pruritus has occurred in other pregnancies and then disappeared immediately after delivery. In a first pregnancy, diagnosis is generally made on clinical grounds alone and can be confirmed only with the rapid postpartum disappearance of the pruritus.

The pruritus affects all parts of the body, is worse at night, and may be so severe that the patient is suicidal. Excoriations are usually obvious, and occasionally the cholestasis is complicated by diarrhea or steatorrhea. Jaundice occurs in 10% to 25% of patients and usually follows the onset of pruritus by 2 to 4 weeks. Jaundice without pruritus is rare. Occasionally, the affected patient will be receiving progesterone therapy.

Variable levels of transaminases are seen in ICP, from mild to 10- to 20-fold increases. The concentration of bilirubin usually increases less than 5 mg/dL. The serum level of alkaline

phosphatase is less helpful in pregnancy. The most specific and sensitive marker of ICP is the serum level of bile acid, which is always increased in this condition, can be 100 times above normal, and may correlate with fetal risk. Liver biopsy is needed only if a more serious liver disease is strongly suspected clinically. In ICP, the liver has a nearly normal appearance, with mild cholestasis and minimal or no hepatocellular necrosis.

Management

With ICP, the main risk is to the fetus and includes premature delivery (up to 60% of cases), perinatal death, and fetal distress. For the fetus, this is a high-risk pregnancy. Fetal monitoring for chronic placental insufficiency is essential but does not prevent all fetal deaths. Acute anoxic injury can be prevented only by delivery as soon as the fetus is mature. A Swedish population study of more than 45,000 pregnancies with 693 cases of ICP (1.3%) showed that fetal complications correlated with the increase in maternal levels of bile acid, and premature delivery, asphyxial events, and meconium staining occurred only when maternal bile acid levels were more than 40 μmol/L. Whether maternal therapy with ursodeoxycholic acid (UDCA) will improve fetal outcome is not known.

Pruritus and liver dysfunction resolve immediately after delivery, with no maternal mortality; however, some patients are severely distressed, even suicidal, because of the pruritus. Management strategies for the mother have focused on symptomatic relief. Withdrawal of exogenous progesterone has produced remission of the pruritus in some patients before delivery.

UDCA is the agent of choice for the treatment of ICP. UDCA, 10 to 20 mg/kg daily, successfully relieves pruritus, with parallel improvement in liver test results, and it has no adverse maternal or fetal effects. In 1 study, fetal outcome was improved, with fewer premature births. High-dose UDCA, 1.5 to 2.0 g daily, has been shown to relieve pruritus in most cases, to decrease abnormal maternal levels of bile acid, and to be completely safe for the fetus. Moreover, babies born to these mothers had bile acid levels that were closer to normal than those of untreated mothers. In randomized controlled trials, UDCA has been shown to be more effective and safer than cholestyramine, more effective than dexamethasone (although dexamethasone has the advantage of promoting fetal lung maturity), and more effective than S-adenosyl-L-methionine. Epomediol and silymarin have produced symptomatic but not biochemical relief in a few patients.

ICP recurs in 45% to 70% of subsequent pregnancies, and it occurs occasionally in nonpregnant women who take oral contraceptives. Patients with ICP are subsequently at higher risk than the general population for gallstones and cholecystitis, nonalcoholic pancreatitis, nonalcoholic cirrhosis, and hepatitis C. Some rare familial cases of apparent ICP have persisted postpartum, with progression to subsequent fibrosis and cirrhosis.

Preeclampsia

Preeclampsia is the triad of hypertension, edema, and proteinuria in the third trimester of pregnancy. It occurs in 5% to 10% of pregnancies, but the liver is involved in only a small proportion of patients. It is the most common cause of liver tenderness and abnormal liver test results in pregnant patients. The cause of preeclampsia appears to involve defective placentation that leads to generalized endothelial dysfunction.

Clinical Features

Patients with preeclampsia may present with right upper abdominal pain, jaundice, and a tender liver of normal size. Increases in transaminase levels vary from mild to 10- to 20-fold. The bilirubin concentration is usually less than 5 mg/dL. Involvement of the liver always indicates severe preeclampsia.

Management

No specific therapy is needed for the liver involvement of preeclampsia, and its only importance is that it indicates severe disease and the need for immediate delivery to avoid eclampsia and liver rupture or necrosis. HELLP syndrome and AFLP may complicate preeclampsia.

HELLP Syndrome

Severe preeclampsia is complicated in 2% to 12% of cases (0.2%-0.6% of all pregnancies) by HELLP syndrome, which is characterized by hemolysis, elevated liver enzymes, and a low platelet count. Although this syndrome has been recognized for more than 50 years, its diagnosis, management, and pregnancy outcome are still matters of controversy.

Clinical Features and Diagnosis

No diagnostic clinical features differentiate HELLP syndrome from preeclampsia. Most patients with HELLP syndrome present with epigastric or right upper quadrant pain (65%-90% of patients), nausea and vomiting (35%-50%), a "flulike" illness (90%), and headache (30%). They usually have edema and weight gain (60% of patients), right upper quadrant tenderness (80%), and hypertension (80%); jaundice is uncommon (5%). Some patients have no obvious preeclampsia. Most patients (71%) present between 27 and 36 weeks of gestation, but presentation can be earlier or up to 48 hours after delivery. HELLP syndrome is more common in multiparous patients and older patients.

With the presence of microangiopathic hemolytic anemia, the characteristic histologic finding in both HELLP syndrome and preeclampsia is periportal hemorrhage and fibrin deposition. Periportal hepatocytes are necrotic, and thrombi may form in small portal arterioles. Severe disease may have diffuse or multiple areas of infarction; hemorrhage dissects through the portal connective tissue initially from zone 1, then more diffusely to involve the whole lobule, leading to large hematomas, capsular tears, and intraperitoneal bleeding. Liver biopsy is rarely needed for diagnosis.

The diagnosis of HELLP syndrome must be established quickly because of the maternal and fetal risk and the necessity for immediate delivery. Diagnosis requires the presence of all 3 criteria: 1) hemolysis with an abnormal blood smear, an increased lactate dehydrogenase level (>600 U/L), and an increased indirect bilirubin level; 2) an aspartate aminotransferase level of more than 70 U/L; and 3) a platelet count less than 100×10^3/μL and, in severe cases, less than 50×10^3/μL (Table 34.4). These diagnostic criteria, however, are not applied consistently. Prothrombin time, activated partial thromboplastin time, and fibrinogen levels are usually normal, with no increase in fibrin-split products, but occasionally disseminated intravascular coagulation may be present. The increase in transaminase levels can vary from mild to 10- to 20-fold, and the bilirubin concentration is usually less than 5 mg/dL. Computed tomography (with

Table 34.4. Classification of HELLP Syndrome

Class	*Platelets, ×10³/μL*	*AST, U/L*	*LDH, U/L*[a]
I	<50	>70	>600
II	50-100	>70	>600
III	100-150	>70	>600

Abbreviations: AST, aspartate aminotransferase; HELLP, hemolysis, elevated liver enzymes, and low platelet count; LDH, lactate dehydrogenase.
[a] Required hemolysis criteria are hemolysis on blood smear, elevated LDH, and increased indirect bilirubin.

limited views) is indicated for patients with HELLP syndrome to detect liver rupture, subcapsular hematomas, intraparenchymal hemorrhage, or infarction (Figure 34.1); these abnormalities may correlate with the decrease in platelet count but not with the liver test abnormalities.

Management

The first priority in the management of patients with HELLP syndrome is antepartum stabilization of the mother, with treatment of hypertension and disseminated intravascular coagulation and seizure prophylaxis. If possible, the patient should be transferred to a tertiary referral center and computed tomography of the abdomen (with limited views) performed.

Delivery is the only definitive therapy. If the patient is beyond 34 weeks of gestation or has multiorgan failure, disseminated intravascular coagulation, kidney failure, abruptio placentae, or fetal distress, immediate delivery should be performed, probably by cesarean delivery, but well-established labor should be allowed to proceed if there are no obstetric complications or disseminated intravascular coagulation. Many patients (40%-50%) require cesarean delivery, especially if they are primigravida remote from term with a cervix that is unfavorable. Half the patients require blood or blood products to correct hypovolemia, anemia, or coagulopathy. Management remote from term is more controversial, especially if the fetal lungs are immature and the maternal physiologic condition is stable and mild. A National Institutes of Health Consensus Development Panel has suggested that perinatal outcome at less than 34 weeks of gestation is better when corticosteroids (betamethasone or dexamethasone, which cross the placenta) are administered for 24 to 48 hours, with delivery thereafter. The main benefit of this therapy is fetal lung maturity, but in some cases it also improves the maternal platelet count. Some advocate giving dexamethasone to all women with HELLP syndrome, starting treatment before delivery but completing it postpartum, with no delay in delivery, and corticosteroids may aid maternal physiologic stability during the transfer time to a tertiary referral center. With longer conservative therapy, the condition of most women with HELLP syndrome deteriorates in 1 to 10 days after diagnosis, with a high risk of fetal loss.

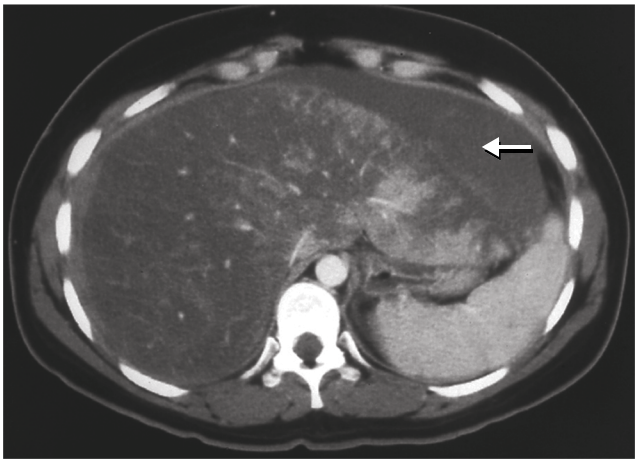

Figure 34.1. Computed Tomogram of the Abdomen. The patient is a 28-year-old woman with severe HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome at 39 weeks' gestation. A large subcapsular hematoma (arrow) extends over the left lobe; the right lobe has a heterogeneous, hypodense appearance because of widespread necrosis, with "sparing" of the areas of the left lobe (compare perfusion with the normal spleen).

In most patients, HELLP syndrome resolves rapidly and early after delivery, and the platelet count normalizes by 5 days, but some have persisting thrombocytopenia, hemolysis, and progressive increases in bilirubin and creatinine levels. The persistence of signs for more than 72 hours, without improvement or the development of life-threatening complications, is usually an indication for plasmapheresis. Many different treatment modalities have been used, including plasma volume expansion, antithrombotic agents, corticosteroids, plasmapheresis, plasma exchange with fresh frozen plasma, and dialysis, but no clinical trials have been conducted.

Serious maternal complications are common in HELLP syndrome, including disseminated intravascular coagulation (20% of patients), abruptio placentae (16%), acute kidney failure (8%), pulmonary edema (8%), acute respiratory distress syndrome (1%), severe ascites (8%), liver failure (2%), eclampsia, and wound hematomas. Maternal mortality rates range from 1% to 25%. Once delivered, most babies do well.

Generally, hepatic hemorrhage without rupture is managed conservatively in hemodynamically stable patients, but patients need close hemodynamic monitoring in an intensive care unit, correction of coagulopathy, immediate availability of large-volume transfusion of blood and blood products, immediate intervention for rupture, and follow-up diagnostic computed tomographic studies as needed. Exogenous trauma, including abdominal palpation, convulsions, emesis, and unnecessary transportation must be avoided.

Liver rupture is a rare, life-threatening complication of HELLP syndrome. It usually is preceded by an intraparenchymal hemorrhage that progresses to a contained subcapsular hematoma in the right lobe. The capsule then ruptures, with hemorrhage into the peritoneum. Survival depends on rapid and aggressive medical management and immediate surgery, although the best surgical management is still debated. The options include evacuation of the hematoma with packing and drainage, ligation of the hepatic artery, partial hepatectomy, direct pressure, packing or hemostatic wrapping, application of topical hemostatic agents, oversewing of the laceration, and angiographic embolization. Preoperatively, aggressive supportive management of hypovolemia, thrombocytopenia, and coagulopathy is essential. Maternal mortality from liver rupture is high at 50%, and perinatal mortality rates are 10% to 60%, mostly from placental rupture, intrauterine asphyxia, or prematurity.

The risk of recurrence of HELLP syndrome in subsequent pregnancies is difficult to assess from the data available; the reported incidence is 4% to 25%. Patients with subsequent deliveries have a significantly increased risk of preeclampsia, preterm delivery, intrauterine growth retardation, and abruptio placentae.

Acute Fatty Liver of Pregnancy

AFLP is a sudden catastrophic illness that occurs almost exclusively in the third trimester and in which microvesicular fatty infiltration results in encephalopathy and liver failure.

Incidence and Cause

The cause of AFLP may involve abnormalities in intramitochondrial fatty acid oxidation. Mitochondrial trifunctional protein and its α-subunit, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), are 2 enzymes essential for the β-oxidation of fatty acids in liver mitochondria. Autosomally inherited genetic mutations affecting these 2 enzymes are associated most closely with AFLP, especially the G1548C mutation for LCHAD deficiency. The mothers of babies with defects in fatty acid oxidation and mothers within families with known defects in fatty acid oxidation have a high incidence (62% in 1 series) of maternal liver disease, either AFLP or HELLP syndrome. LCHAD deficiency has been identified in 20% of babies of mothers with AFLP but not in babies of mothers with HELLP syndrome. It has been speculated that maternal heterozygosity for LCHAD deficiency decreases the maternal capacity to oxidize long-chain fatty acids in both the liver and the placenta. This, together with the metabolic stress of pregnancy and fetal homozygosity for LCHAD deficiency, causes potentially hepatotoxic metabolites of LCHAD to accumulate in the maternal circulation. Perhaps external factors exacerbate this situation. There are reports of maternal liver disease associated with defects of other enzymes involved in fatty acid oxidation, but the role of these other enzymes in causing AFLP is a matter of controversy.

Clinical Features and Diagnosis

Unlike patients with HELLP syndrome, 50% of patients with AFLP are nulliparous, with an increased incidence of twin pregnancies. AFLP occurs almost exclusively in the third trimester, from 28 to 40 weeks, most commonly at 36 weeks. For a few patients, the presentation is jaundice in the postpartum period. The usual presentation varies from asymptomatic to acute liver failure, but most patients have jaundice. A typical patient has 1 to 2 weeks of anorexia, nausea, vomiting, and right upper quadrant pain and looks ill, with jaundice, hypertension, edema, ascites, a small liver (it may be enlarged initially), and various degrees of hepatic encephalopathy. Intrauterine death may occur. About 50% of patients with AFLP have preeclampsia.

In AFLP, the serum level of aspartate aminotransferase varies from near normal to 1,000 U/L; it is usually about 300 U/L. The bilirubin concentration is usually less than 5 mg/dL but higher in severe or complicated disease. Other typical abnormalities are normochromic, normocytic anemia; high leukocyte count; normal to low platelet count; abnormal prothrombin time, activated partial thromboplastin time, and fibrinogen, with or without disseminated intravascular coagulation; metabolic acidosis; kidney dysfunction (often progressing to oliguric kidney failure); hypoglycemia; high ammonia level; and, often, biochemical pancreatitis. Computed tomography is more sensitive than ultrasonography for detecting AFLP. A definitive diagnosis of AFLP can be made only on the basis of the typical histologic features found on liver biopsy. In the clinical setting, a presumptive diagnosis of AFLP is usually made and the baby is delivered as soon as possible. The histologic appearance of AFLP is microvesicular and, infrequently, macrovesicular fatty infiltration, which is most prominent in zone 3; this fat consists of free fatty acids. Also, there is lobular disarray, with pleomorphism of hepatocytes and mild portal inflammation with cholestasis, an appearance similar to that of Reye syndrome and tetracycline and valproic acid toxicity (Figure 34.2). Although the histologic features usually are diagnostic of AFLP, occasionally, they cannot be differentiated from those of viral hepatitis or preeclampsia.

For severely ill patients with liver failure in the third trimester, the differential diagnosis includes AFLP, HELLP syndrome (Table 34.5), thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and fulminant viral hepatitis.

Management

Early recognition of AFLP, with immediate termination of the pregnancy and intensive supportive care, is essential for the survival of both the mother and the fetus. Recovery before delivery has not been reported. Although the inciting injury ceases with delivery, the patient requires support until liver function has time to recover. By 2 to 3 days after delivery, the transaminase levels and encephalopathy improve, but intensive supportive care is needed to manage the many complications of liver failure until this recovery occurs. Patients who are critically ill at the time of presentation, who have complications (encephalopathy, hypoglycemia, coagulopathy, or bleeding [or a combination of these]),

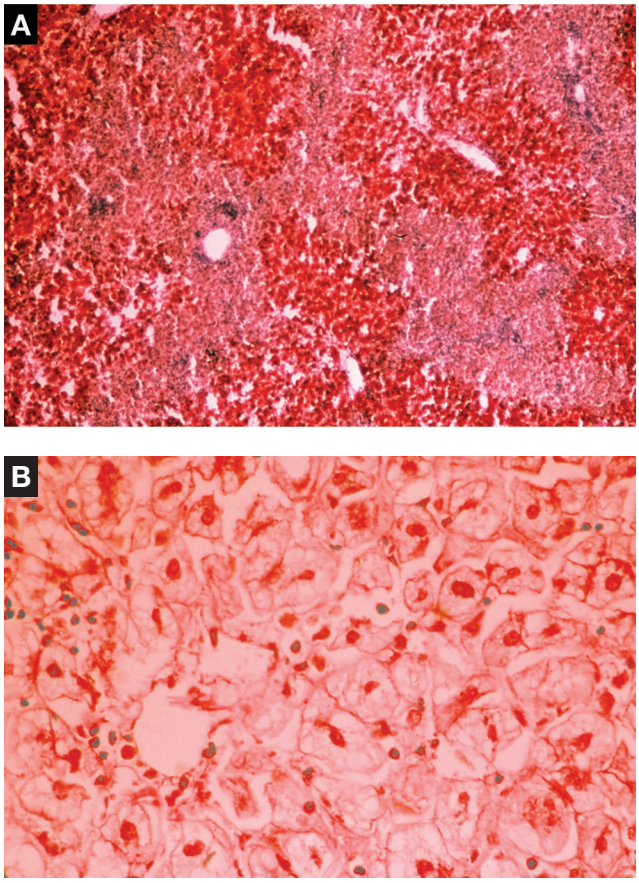

Figure 34.2. Histologic Appearance of the Liver in Acute Fatty Liver of Pregnancy. The patient is a 32-year-old primigravida. A, Sudan stain (low power) shows diffuse fatty infiltration (red staining) involving predominantly zone 3, with relative sparing of periportal areas. B, Hematoxylin-eosin stain (high power) shows hepatocytes stuffed with microvesicular fat (free fatty acids) and centrally located nuclei.

Table 34.5. Diagnostic Differences Between AFLP and HELLP Syndrome

Feature	*AFLP*	*HELLP*
Parity	Nulliparous, twins	Multiparous, older
Jaundice	Common	Uncommon
Total bilirubin, mean, mg/dL	8	2
Encephalopathy	Present	Absent
Platelet count	Low normal	Low
Prothrombin time	Prolonged	Normal
aPTT	Prolonged	Normal
Fibrinogen	Low	Normal or increased
Glucose	Low	Normal
Creatinine	High	High
Ammonia	High	Normal
Computed tomography	Fatty infiltration	Hemorrhage

Abbreviations: AFLP, acute fatty liver of pregnancy; aPTT, activated partial thromboplastin time; HELLP, hemolysis, elevated liver enzymes, and low platelet count.

or whose condition continues to deteriorate despite emergency delivery, should be transferred to a liver center.

Delivery is usually by cesarean delivery, but the necessity for this has not been tested in randomized trials. Rapid controlled vaginal delivery with fetal monitoring is probably safer if the cervix is favorable and will decrease the incidence of major intra-abdominal bleeding. It probably is best to maintain an international normalized ratio of less than 1.5 and a platelet count of more than 50×10^3/μL during and after delivery and to provide antibiotic prophylaxis. With correction of the coagulopathy, epidural anesthesia is probably the best choice and will allow a better ongoing assessment of the patient's level of consciousness.

Intensive supportive care is the same as for any patient with acute liver failure. Plasmapheresis has been used in some cases, but its benefit is unproven. Corticosteroids are ineffective. Although liver function starts to improve within 3 days after delivery, the disease then enters a cholestatic phase, with increasing levels of bilirubin and alkaline phosphatase. Depending on the severity and complications, recovery can occur in days or be delayed for months. It is complete when the patient has no signs of chronic liver disease. With advances in supportive management of these patients, including early delivery, the maternal mortality rate is currently 10% to 18% and the fetal mortality rate is 9% to 23%. Infectious and bleeding complications are the most life-threatening conditions. Liver transplant has a very limited role in AFLP because of the great potential for recovery with delivery, but it should be considered for patients whose clinical course continues to deteriorate with advancing acute liver failure after the first 1 or 2 days postpartum without signs of liver regeneration.

Many patients do not become pregnant again after AFLP, either by choice, because of the devastating effect of the illness, or by necessity, because of the hysterectomy to control postpartum bleeding. Women who are carriers of the mutation for LCHAD deficiency have an increased risk of recurrence of AFLP in 20% to 70% of pregnancies. All babies of mothers with AFLP are tested for defects of fatty acid oxidation because presymptomatic diagnosis and appropriate early management reduces morbidity and mortality among these babies. More extensive neonatal screening for defects of fatty acid oxidation is advocated by some. For mothers without identifiable abnormalities of fatty acid oxidation, AFLP does not tend to recur in subsequent pregnancies, although rare cases have been reported.

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35

Liver Transplantation

J. EILEEN HAY, MB, ChB

Orthotopic liver transplant (OLT) is highly effective for patients with liver failure, restoring normal health and a normal lifestyle. Patient survival is excellent; nationally, the survival rate is 86% at 1 year after OLT and 72% at 5 years. Timely evaluation for transplant and optimization of pretransplant care is essential for the potential liver recipient. However, the demand for donor organs greatly exceeds supply. In the United States in 2012, about 5,000 deceased donor organs and only 200 living donor organs were available; currently, over 16,000 patients are on the liver transplant list. Patient selection and organ allocation are 2 major problems.

Indications for OLT

Decompensated cirrhosis is the most common indication for OLT (about 70% of cases) (Box 35.1). The most common underlying liver disease that leads to OLT in the United States is cirrhosis due to hepatitis C (41% of cases), with or without hepatocellular carcinoma, followed by alcoholic cirrhosis (14%), chronic cholestatic liver disease (primary biliary cirrhosis and primary sclerosing cholangitis) (14%), and cryptogenic cirrhosis (10%) (some cases of cryptogenic cirrhosis may be due to nonalcoholic fatty liver disease), with all other causes of cirrhosis being less common. This distribution of causes of liver disease that leads to OLT will likely change over the next decades, with the number of cases of hepatitis C decreasing but the number of cases of obesity-related liver disease increasing. The complications of cirrhosis that are accepted indications for OLT are hepatocellular carcinoma, hepatopulmonary syndrome, and portopulmonary hypertension. The following criteria (the Milan criteria) are used to select tumors suitable for OLT (ie, those likely to be cured by OLT): a single tumor 5 cm or less in any dimension or 3 or fewer lesions, each no larger than 3 cm. For all these tumors, there can be no evidence of vascular invasion or extrahepatic spread.

About 5% of all OLT in the United States is performed for acute medical emergencies: acute liver failure, fulminant Wilson disease, or early failure of a liver allograft (primary nonfunction or hepatic artery thrombosis within the first postoperative week). Acute liver failure is an uncommon condition, with only about 3,000 cases annually in the United States. The most frequent cause is acetaminophen hepatotoxicity (almost half of all cases), followed by indeterminate causes (20%) and idiosyncratic drug reactions (14%). Other recognized indications for OLT in adults are primary hyperoxaluria, familial amyloidosis, and cystic fibrosis, diseases in which the metabolic defect is in the liver. For children, several other metabolic diseases are indications for OLT. Cholangiocarcinoma after intensive radiotherapy and chemotherapy is a newly accepted indication for OLT. Controversy continues to surround several proposed indications for OLT, including metastatic neuroendocrine tumors and polycystic liver disease. Occasionally, in some regions of the United States, OLT is performed for these indications.

Allocation of Organs

In February 2002, the allocation system for deceased donor livers in the United States was changed to a system based on short-term mortality; that is, an organ is allocated to the patient most likely to die in the next 3 months (Table 35.1). The most urgent indication for OLT is acute liver failure, and these patients are given

Abbreviations: DCD, donated after cardiac death; INR, international normalized ratio; LDLT, living donor liver transplant; MELD, Model for End-stage Liver Disease; OLT, orthotopic liver transplant; UNOS, United Network for Organ Sharing

Box 35.1. Indications for Orthotopic Liver Transplant

- **Cirrhosis of any cause**
- **Cirrhotic complications**
  - Hepatocellular carcinoma
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension
- **Acute liver failure from fulminant Wilson disease**
- **Primary nonfunction or early hepatic artery thrombosis of hepatic allograft**
- **Metabolic diseases**
  - Hyperoxaluria
  - Familial amyloidosis
  - Cystic fibrosis
- **Cholangiocarcinoma**

the highest priority for urgent organ allocation (status 1 patients). Unlike status 1 patients, who should be assigned an organ quickly after activation, patients with chronic liver disease generally have a 2-step process: listing for OLT and allocation of a donor organ. If otherwise suitable to be a transplant recipient, a patient with cirrhosis will be registered with the United Network for Organ Sharing (UNOS) on the liver transplant waiting list; however, organ allocation is prioritized for patients listed within each ABO blood group, according to their 3-month expected mortality, as defined by the Model for End-stage Liver Disease (MELD) scoring system.

The MELD score is based on serum levels of creatinine and bilirubin and the international normalized ratio (INR). It is calculated according to the following formula:

$$\begin{aligned}\text{MELD Score} = {} & 0.957 \times \log_2 \text{Creatinine}\ (\text{mg/dL}) \\ & + 0.378 \times \log_2 \text{Bilirubin}\ (\text{mg/dL}) \\ & + 1.120 \times \log_2 \text{INR} + 0.643\end{aligned}$$

Table 35.1. Allocation of Deceased Donor Organs

Allocation Status	*Disease Category*
Status 1	Acute liver failure
	Fulminant Wilson disease
	Primary nonfunction of allograft
	Hepatic artery thrombosis (<1 wk after transplant)
MELD score, calculated	Cirrhosis from any cause
MELD score, assigned	Hepatocellular carcinoma
	Hepatopulmonary syndrome
	Hyperoxaluria
	Familial amyloidosis
	Portopulmonary hypertension
	Cholangiocarcinoma
	Cystic fibrosis
	Appeal to regional review board[a]

Abbreviation: MELD, Model for End-stage Liver Disease.
[a] Any transplant program can appeal to the regional review board for an assigned MELD score for any patient to allow the patient to receive an organ.

The 3 biochemical variables are entered into a computer program, and the MELD score is calculated (http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-model-unos-modification). For patients with MELD scores higher than 40, the expected 3-month mortality rate is 80% without OLT; for patients with scores of 20 to 29, the rate is 20% to 25%; and for patients with scores less than 10, there is no excess short-term mortality.

Hepatocellular carcinoma is an accepted indication for OLT even though mortality is not reflected by the MELD score. A patient with hepatocellular carcinoma within the Milan criteria is assigned a MELD score to allow OLT in 3 to 12 months (called a *MELD exception*). In the United States, the other MELD exceptions for adults are hepatopulmonary syndrome, hyperoxaluria, familial amyloidosis, cholangiocarcinoma, cystic fibrosis, and portopulmonary hypertension. For all these MELD exceptions, there are strict inclusion and exclusion criteria (www.unos.org). Patients with these criteria are assigned a MELD score of 22 (except for patients with hyperoxaluria, who are assigned a score of 28), with a 10% mortality equivalent increase every 3 months.

The only ways for patients to be guaranteed consideration for allocation of a deceased donor organ are to have status 1, have a calculated MELD score, or have an assigned MELD score (ie, for MELD exceptions). For controversial indications for OLT or for patients who are more symptomatic than suggested by their MELD score, transplant programs may appeal to their regional review board to be given an assigned MELD score that will allow early OLT. Different review boards have different philosophies about which patients will be considered for an assigned MELD score; there are no national rules for these review boards.

Despite the success of OLT, the procedure has some absolute and relative contraindications (Box 35.2). None of the relative contraindications are absolute, and their weight may vary in different transplant programs; however, added together, they may preclude a patient from having OLT.

Box 35.2. Contraindications to Orthotopic Liver Transplant

- **Absolute contraindications**
  - Extrahepatic malignancy unless tumor-free for ≥2 y and low probability of recurrence
  - Untreated alcoholism or alcoholic hepatitis
  - High-dose or multiple pressors
  - Severe multiorgan failure
  - Severe psychologic disease likely to affect adherence to therapy
  - Severe pulmonary hypertension
  - Advanced cardiopulmonary disease
- **Relative contraindications**
  - General debility
  - Social isolation
  - Advanced age
  - Extensive previous abdominal surgery
  - Extensive portal or mesenteric thrombosis

Immunosuppression

Five main groups of immunosuppressive medications are used in OLT (Table 35.2). Each immunosuppressive drug has its own site of action and adverse effects. The risk of rejection is highest in the first weeks after OLT, when immunosuppression is at its highest level. Tacrolimus has replaced cyclosporine as the calcineurin inhibitor of choice in most liver transplant programs. Frequently, corticosteroids with or without mycophenolate mofetil are administered in the first postoperative weeks. Immunosuppression is tapered by 4 months, often to tacrolimus monotherapy, with lower serum levels. Long-term calcineurin inhibitor monotherapy is ideal, but if nephrotoxicity develops in response to the treatment, low-dose calcineurin inhibitor plus mycophenolate mofetil or sirolimus may be used. Overall, the trend now is to tailor immunosuppression to each patient, depending on the time from OLT, rejection history, and adverse effects from individual drugs. Newer agents are being sought to avoid renal and metabolic dysfunction.

Complications After OLT

Primary Nonfunction of the Liver Allograft

The most dire early complication is primary nonfunction of the allograft. This starts immediately with the appearance of clear bile or no output of bile, high aminotransferase levels, and then an increase in bilirubin concentration. The main identified risk factor is high fat content of the allograft. Grafts may be biopsied to assess this before implantation. No therapy is available for primary nonfunction, and the patient's status needs to be reactivated as status 1 for the patient to receive a second graft.

Hepatic Artery Thrombosis

Another dreaded early complication of OLT is hepatic artery thrombosis. This is most common in children, size-mismatched grafts, and living donor OLT. It usually occurs in the first week after OLT, but it can develop later. The clinical manifestations may be subtle, and patients may be asymptomatic or have mild fever or increased aminotransferase levels. In the majority of adults with hepatic artery thrombosis, the grafts fail because of hepatic necrosis or ischemic cholangiopathy. When hepatic artery thrombosis occurs in the first 7 days after OLT, the patient will be listed for retransplant as status 1.

Cellular Rejection

Acute cellular rejection occurs in up to 50% of liver recipients and usually is associated with mild to moderate biochemical abnormalities and, occasionally, fever. Although the diagnosis can be suspected by the timing in the early weeks after OLT, definitive diagnosis requires histologic examination of the liver, with the following findings: 1) portal infiltrates with activated lymphocytes and some eosinophils, 2) lymphocytic cholangitis, and 3) venous endotheliitis. Ninety percent of cases of rejection occur in the first 2 postoperative months. Most rejections are treated with intravenous corticosteroids, and 85% of patients with rejection have a response to corticosteroids. Of the cases of steroid-resistant rejection, 90% respond to intravenous antibody therapy with antithymocyte globulin. Acute cellular rejection early after OLT generally has no effect on long-term graft outcome, except for patients with hepatitis C, and very few grafts are lost to chronic rejection.

Biliary Strictures

The biliary anastomosis, either duct-to-duct or biliary-enteric anastomosis, is the most common site of biliary strictures, which usually form in the first month. Most strictures respond to endoscopic dilatation, with or without stents, but occasionally surgical revision of the anastomosis is needed.

Nonanastomotic or ischemic-type biliary strictures may form at any time, but the median time is about the eleventh postoperative week. The most common identified cause is hepatic artery thrombosis, either early or late. Other associations are with ABO incompatibility, long warm (>90 minutes) or cold (>12 hours) ischemia time, and grafts donated after cardiac death (DCD). Some of these strictures can be managed with endoscopic or percutaneous biliary stenting, although ischemic-type biliary stricturing leads to death or a need for retransplant in about 50% of cases.

Infections

A systemic fungal, viral, or bacterial infection develops in 1 in 5 liver transplant recipients during the first postoperative month. Cytomegalovirus infection is the most common viral infection. Its incidence peaks in the first 3 to 5 postoperative weeks, and it is rare after the first year. Its presence is suggested by fever and leukopenia. Treatment is with intravenous ganciclovir or oral

Table 35.2. Immunosuppressive Drugs and Their Adverse Effects

Drug Class	*Drug*	*Adverse Effects*
Corticosteroids[a]	Methylprednisolone Prednisone	Hypertension, diabetes mellitus, neurotoxicity, hyperlipidemia, bone loss, myopathy
Purine antagonists	Azathioprine Mycophenolate mofetil	Cytopenias Gastrointestinal adverse effects (mycophenolate mofetil only)
Calcineurin inhibitors[a,b]	Tacrolimus Cyclosporine	Nephrotoxicity, hypertension, diabetes mellitus, neurotoxicity
TOR inhibitors	Sirolimus (rapamycin)	Cytopenias, hyperlipidemia, poor wound healing, hepatic artery thrombosis
Antibody therapy (intravenous)[a]	Antithymocyte globulin (thymoglobulin) Basiliximab	Profound immunosuppression, opportunistic infections

Abbreviation: TOR, target of rapamycin.

[a] Used for treatment and prevention of rejection (others used only for prevention).

[b] Beware of drug interactions with drugs affecting the cytochrome P450 enzyme system: Drugs inhibiting the cytochrome P450 system (eg, fluconazole) increase the levels of calcineurin inhibitors, and drugs stimulating the cytochrome P450 system (eg, phenytoin) decrease calcineurin inhibitor levels and thus increase the risk of rejection.

valganciclovir. *Candida* infection is the most common fungal infection, although opportunistic infections can also be seen with *Aspergillus, Nocardia, Cryptococcus*, and *Pneumocystis*. Many transplant programs provide prophylaxis for *Pneumocystis* in the early postoperative months when immunosuppression is at its highest level.

Late Complications

The main late complications after OLT are recurrent disease, complications of immunosuppression, and de novo malignancies.

When late allograft dysfunction occurs in a patient who is well and receiving stable, therapeutic immunosuppression, recurrent disease is the most likely diagnosis, especially if the underlying cause of liver disease is hepatitis C. The diagnosis is histologic, and liver biopsy is needed. The incidence and potential severity of recurrent disease in an allograft is greatest for hepatitis C. Treatment of recurrent hepatitis C with peginterferon and ribavirin results in a sustained virologic response in about 30% of patients. For genotype 1 disease, a newer anti–hepatitis C virus agents may be used, although adverse effects are common and there are limited data on safety or efficacy. Recurrent hepatitis B is prevented in more than 90% of patients by hepatitis B immunoglobulin and antiviral therapy. However, most other liver diseases, including primary biliary cirrhosis and primary sclerosing cholangitis, autoimmune hepatitis, nonalcoholic fatty liver disease, and hepatocellular carcinoma, may recur.

Most OLT recipients have normal cardiac function, but increasingly patients who are obese or have diabetes mellitus or hypertension are undergoing OLT. In addition, even in those with no risk factors for coronary artery disease before OLT, treatment with immunosuppressive drugs may produce an increase in hypertension, diabetes mellitus, kidney failure, dyslipidemia, and obesity in a high percentage of patients (Table 35.3). This leads to a high risk of cardiovascular diseases for many OLT recipients, with cyclosporine having more metabolic effects than tacrolimus. OLT recipients must receive adequate screening and therapy for these risk factors.

Liver transplant recipients have multiple potential risk factors for cancer: immunosuppression, viruses (hepatitis C virus, hepatitis B virus, human papillomavirus, human herpesvirus 6, Epstein-Barr virus), alcohol use, and smoking. Furthermore, now many recipients are older than 60 years at the time of OLT and, thus, have the increased cancer risk of aging. The effect of immunosuppression probably is related to the degree of immunosuppression rather than to individual agents. Depending on the series, the reported overall incidence of cancer varies from 2.9% to 14%; the reported cancer-related mortality rate is 0.6% to 8%. Malignancies are an important cause of long-term mortality.

Malignancies that occur frequently in OLT recipients are skin cancers, posttransplant lymphoproliferative disease, and cervical, vulvar, and anal squamous cancers. The incidence of colorectal cancer is increased only for recipients with primary sclerosing cholangitis, likely related to ulcerative colitis. Increasingly, data show notable mortality at 5 to 10 years after OLT from upper aerodigestive cancers in recipients who continue to smoke and drink.

Table 35.3. Cardiovascular Risk Factors in Liver Recipients

Complication	*Recipients Affected, %*
Hypertension[a]	50
Diabetes mellitus	30 (15, new onset)
Kidney failure[a]	14-30
Dyslipidemia[a]	30-45
Obesity	20-30

[a] Worse with cyclosporine than with tacrolimus.

Expansion of the Donor Pool

Adult-to-adult living donor liver transplant (LDLT) uses the right lobe of the donor for implant into the recipient. For pediatric recipients, the left lobe may be used, depending on size. The major advantages of LDLT over deceased donor transplant are availability of the organ and expansion of the donor pool. LDLT produces more vascular and biliary problems but no less rejection. The donor morbidity rate is 8% to 26%, and the mortality rate is 0.3%. Other ways of expanding the donor pool are the use of older donors (higher rate of primary nonfunction), split livers (higher complication rate, labor-intensive procedure, and disadvantage for the primary recipient), marginal donors (eg, fatty liver with an increased risk of primary nonfunction), DCD graft (increased risk of biliary complications), and high-risk donors (high-risk lifestyle or medical history).

Suggested Reading

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Questions and Answers

Questions

Abbreviations used:

ALP, alkaline phosphatase
ALT, alanine aminotransferase
AMA, antimitochondrial antibody
ANA, antinuclear antibody
anti-HAV, antibody to hepatitis A virus
anti-HBc, antibody to hepatitis B core antigen
anti-HBe, antibody to hepatitis B e antigen
anti-HBs, antibody to hepatitis B surface antigen
anti-HCV, anti–hepatitis C virus
ASH, alcoholic steatohepatitis
AST, aspartate aminotransferase
BMI, body mass index
CA19-9, carbohydrate antigen 19-9
CBC, complete blood cell count
CMV, cytomegalovirus
CT, computed tomography
CYP, cytochrome P450
DILI, drug-induced liver injury
DILIN, Drug-Induced Liver Injury Network
EBV, Epstein-Barr virus
ECOG, Eastern Cooperative Oncology Group
EGD, esophagogastroduodenoscopy
ERCP, endoscopic retrograde cholangiopancreatography
FDA, US Food and Drug Administration
GAVE, gastric antral vascular ectasia
GGT, γ-glutamyltransferase
HAT, hepatic artery thrombosis
HBeAg, hepatitis B e antigen
HBsAg, hepatitis B surface antigen
HBV, hepatitis B virus
HCC, hepatocellular carcinoma
HCV, hepatitis C virus
HELLP, hemolysis, elevated liver enzymes, and low platelet count
HEV, hepatitis E virus
HIV, human immunodeficiency virus
IBD, inflammatory bowel disease
ICP, intrahepatic cholestasis of pregnancy
ICU, intensive care unit
INR, international normalized ratio
IV, intravenous
LKM1, anti-liver-kidney microsome type 1
MCV, mean corpuscular volume
MELD, Model for End-stage Liver Disease
MRCP, magnetic resonance cholangiopancreatography
MRI, magnetic resonance imaging
NASH, nonalcoholic steatohepatitis
NHANES, National Health and Nutrition Examination Survey
PBC, primary biliary cirrhosis
PSC, primary sclerosing cholangitis
SMA, smooth muscle antibody
TIPS, transjugular intrahepatic portosystemic shunt
UDCA, ursodeoxycholic acid
ULRR, upper limit of the reference range
WBC, white blood cell

Multiple Choice (choose the best answer)

VI.1. **A 48-year-old woman presents with a 6-month history of fatigue and abnormal liver test results. She had been previously well and denies taking any medications or supplements. She drinks 3 glasses of wine weekly. Physical examination is notable for a BMI of 28 (calculated as weight in kilograms divided by height in meters squared), hepatomegaly, and mild splenomegaly. There are no spider angiomas. Laboratory test results are shown below:**

Component	Result
Hemoglobin, g/dL	14.3
Platelet count, $\times 10^3/\mu L$	140
ALP, U/L	435
ALT, U/L	64
AST, U/L	62
Total bilirubin, mg/dL	1.3
ANA, U (reference range <1.0)	2.8
SMA	1:20
AMA	Negative
γ-Globulin, g/dL (reference range, 0.6-1.6)	1.7

CT showed mild hepatomegaly, mild splenomegaly, periportal lymph nodes at the upper limits of normal in size, and patent abdominal vessels. Which of the following should you advise now?

a. Check for LKM1 autoantibodies
b. Perform ERCP
c. Perform liver biopsy
d. Lose weight and recheck liver enzymes in 1 year
e. Start ursodiol

VI.2. A 34-year-old woman presents with fever and somnolence. She has a history of asthma and has required long-term oral corticosteroids. She was well until 3 days ago, when a fever developed. Today she is sleepy. Her asthma has been stable and her only medications are prednisone 5 mg daily, inhaled fluticasone, fexofenadine, and an oral contraceptive. Physical examination findings include blood pressure 120/60 mm Hg, heart rate 120 beats per minute, and temperature 39°C. The patient had difficulty staying awake during the interview. She is oriented, and there are no focal neurologic abnormalities. Laboratory test results are shown below:

Component	Result
Hemoglobin, g/dL	13
WBC count, /μL	3,000
Segmented neutrophils, %	30
Band forms, %	2
Lymphocytes, %	58
Eosinophils, %	2
AST, U/L	6,200
ALT, U/L	7,500
ALP, U/L	125
Total bilirubin, mg/dL	0.8
Ammonia, μg/dL	25

MRI of the head shows temporal lobe changes. What is the most likely diagnosis?

a. Wilson disease
b. Ischemic liver injury
c. Herpes hepatitis
d. Acetaminophen hepatotoxicity
e. Liver injury to drug or toxin other than acetaminophen

VI.3. A 64-year-old woman presents with worsening liver test results. Two years ago, she had cholecystectomy and was noted to have an abnormal liver. Liver biopsy showed steatohepatitis with mild pericellular fibrosis. Two months ago, she was noted to have an ALT of 66 U/L and mild hyperlipidemia. Simvastatin was initiated; 2 weeks ago, her ALT was 84 U/L. She feels well. Her past history is notable for obesity, diabetes mellitus, and obstructive sleep apnea. Physical examination is notable for obesity and mild hepatomegaly. Laboratory test results are shown below:

Component	Result
CBC	Normal
ALT, U/L	84
AST, U/L	72
ALP, U/L	115
Total bilirubin, mg/dL	1.0
HBsAg	Negative
Anti-HCV	Negative
ANA, U	1.2
SMA	1:20
γ-Globulin, g/dL	1.2

Which of the following should you advise now?

a. HCV RNA test
b. MRCP
c. Liver biopsy
d. Serial monitoring of ALT
e. Cessation of simvastatin

VI.4. A 64-year-old woman has a 6-month history of persistent and stable elevations of liver enzymes. She has a history of hypertension, hypothyroidism, and osteoporosis. She notes dry eyes and dry mouth. Her medications are lisinopril, levothyroxine, alendronate, and aspirin. Examination findings include obesity and hepatomegaly. There are no spider angiomas. Laboratory test results are shown below:

Component	Result
CBC	Normal
ALP, U/L	345
AST, U/L	55
ALT, U/L	73
Total bilirubin, mg/dL	1.5
AMA	Negative
ANA, U	1.5
SMA	1:20
γ-Globulin, g/dL	1.2

Abdominal ultrasonography shows mildly heterogeneous liver echotexture, normal bile ducts, and gallbladder stones in an otherwise normal gallbladder. Liver biopsy shows normal architecture, portal tracts expanded by infiltrate consisting mostly of lymphocytes with few plasma cells, mild lymphocytic cholangitis, no interface activity, and mild steatosis without hepatocellular ballooning. Which of the following should you advise now?

a. Perform MRCP
b. Perform ERCP
c. Administer prednisone and azathioprine
d. Administer ursodiol
e. Observe only, and repeat the liver tests in 3 months

VI.5. A 20-year-old woman presents with persistently abnormal liver test results. Infectious mononucleosis was diagnosed 16 weeks ago when she presented with fatigue and fever. Despite improvement in fever, she has had persistent fatigue and was recently noted to have abnormal levels of liver enzymes. Once weekly, she drinks 3 to 5 alcoholic beverages. She has had 1 sexual partner for the past year; he is well. The patient has no other significant past medical history, and her only medication is an oral contraceptive. Physical examination is notable for a BMI of 22, a liver span of 7 cm, and splenomegaly. Laboratory test results are shown below:

Component	Result
Hemoglobin, g/dL	12.8
Platelet count, $\times 10^3/\mu L$	95
INR	1.6
ALP, U/L	30
AST, U/L	93
ALT, U/L	97
Total bilirubin, mg/dL	0.7
Albumin, g/dL	2.9
ANA, U	2.4
Ceruloplasmin, mg/dL	17
HBsAg, anti-HCV, SMA, and γ-globulin	Negative or normal

Abdominal ultrasonography shows a coarse liver echotexture and mild splenomegaly. Liver biopsy shows lymphoplasmacytic portal inflammation, septal fibrosis with nodular regeneration, mild steatosis, and prominent glycogenated hepatocyte nuclei. Which of the following should you advise next?

a. EBV serologies
b. Heterophile antibody tests (Monospot test)
c. Hepatic copper quantitation
d. Prednisone and azathioprine
e. Vitamin E

VI.6. A 56-year-old man presents with abnormal liver test results. He has experienced fatigue and low-grade fever for 2 months. He took niacin for several years, but he stopped taking it when the liver test results were elevated. Even after niacin was discontinued, the liver test results worsened. His medical history includes hyperlipidemia and bladder cancer treated with intravesical administration of BCG 3 months ago. He works as an accountant. On physical examination, he appears to be a chronically ill man who has a temperature of 38.5°C. The liver is normal on palpation and the spleen is not enlarged. Laboratory test results are shown below:

Component	Result
Hemoglobin, g/dL	12.8
Platelet count, $\times 10^3/\mu L$	423
ALP, U/L	589
ALT, U/L	48
AST, U/L	43
Total bilirubin, mg/dL	0.8
Anti-HCV, HBsAg, ANA, SMA, HIV antibody, tissue transglutaminase antibody	Negative or normal
Blood cultures, chest radiograph, tuberculin skin testing	Negative or normal
Liver ultrasonography	Normal

Liver biopsy shows multiple portal and lobular noncaseating granulomas. What is the most likely diagnosis?

a. *Mycobacterium tuberculosis* infection
b. Atypical mycobacterial infection
c. Granulomatous hepatitis
d. Q fever
e. PBC

VI.7. A 24-year-old woman presents with a recent diagnosis of hepatitis B. She is asymptomatic. She was born in Cambodia and came to the United States at the age of 2 years. Two of her 3 siblings also have hepatitis B. She drinks 1 alcoholic beverage every 6 months. There is no family history of HCC. Her only medication is an oral contraceptive. Physical examination findings are normal. Laboratory test results are shown below:

Component	Result
CBC	Normal
ALT, U/mL	14
HBsAg	Positive
IgG anti-HBc	Positive
HBeAg	Positive
HBV DNA, IU/mL	17 million

Which of the following should you advise?

a. Repeat ALT in 6 months
b. Prescribe entecavir
c. Prescribe lamivudine
d. Prescribe peginterferon
e. Perform liver ultrasonography and monitor alpha fetoprotein levels every 6 months

VI.8. A 35-year-old man has chronic hepatitis B. He came to the United States from Somalia at age 20. He is asymptomatic. His only brother also has hepatitis B. He denies any family history of HCC. Physical examination findings are normal. Diagnostic test results are shown below:

Component	Result
ALT, U/L	20
HBsAg	Positive
IgG anti-HBc	Positive
Anti-HBe	Positive
HBV DNA, IU/mL	2,000
Liver ultrasonography	Normal

Which of the following should you advise?

a. Prescribe lamivudine
b. Prescribe tenofovir
c. Prescribe peginterferon
d. Perform liver ultrasonography every 6 months
e. Perform liver biopsy

VI.9. A 53-year-old man comes for hospital follow-up. He presented with upper gastrointestinal bleeding 8 days ago and had esophageal variceal ligation. Since dismissal 3 days ago, he has done well without further bleeding and denies fluid retention and alterations in mental status. Physical examination is notable for scattered spider angiomas, enlarged left lobe of the liver, and splenomegaly. Laboratory test results are shown below:

Component	Result
Hemoglobin, g/dL	10
Platelet count, $\times 10^3/\mu L$	69
INR	1.2
ALT, U/L	63
Total bilirubin, mg/dL	1.8
Albumin, g/dL	3.1
Creatinine, mg/dL	1.0
HBsAg	Positive
IgG anti-HBc	Positive
Anti-HBe	Positive
HBV DNA, IU/mL	1,900

CT showed a nodular liver, no enhancing liver mass, splenomegaly, and a recanalized umbilical vein. Which of the following should you advise now?

a. Prescribe tenofovir
b. Prescribe peginterferon
c. Perform liver biopsy
d. Create a TIPS
e. Perform liver ultrasonography

VI.10. **A 48-year-old man presents with fever and dark urine. An active urinary sediment was noted, and kidney biopsy demonstrated crescentic glomerulonephritis. On physical examination, he is an ill-appearing man with a temperature of 39.3°C, blood pressure 90/60 mm Hg, and a petechial rash on the anterior surface of both lower extremities. Laboratory test results are shown below:**

Component	Result
Hemoglobin, g/dL	11.3
WBC count, /μL	8,400
Differential count	Normal
Platelet count, $\times 10^3$/μL	134
ALT, U/L	83
Total bilirubin, mg/dL	1.2
Creatinine, mg/dL	2.4
Albumin, g/dL	2.4
HCV RNA, IU/mL	875,000
HCV genotype	1a
Cryoglobulin	Positive
Blood cultures	Negative

Which of the following should you advise now?

a. Prescribe peginterferon, ribavirin, and sofosbuvir
b. Prescribe peginterferon, ribavirin, and rituximab
c. Prescribe plasmapheresis, rituximab, and corticosteroids
d. Prescribe corticosteroids

VI.11. **A 19-year-old woman presents with fatigue and jaundice. She was well until 2 weeks ago when she noted fatigue. Jaundice developed 3 days ago. She started using IV drugs 4 weeks ago. She denies taking any prescribed or over-the-counter medications or supplements. She has no prior history of liver disease. Examination is notable only for jaundice. There are no spider angiomas or splenomegaly. Laboratory test results are shown below:**

Component	Result
Hemoglobin, g/dL	13.5
WBC count, /μL	8,500
Differential count	Normal
Platelet count, $\times 10^3$/μL	223
AST, U/L	965
ALT, U/L	654
Total bilirubin, mg/dL	6.5
Direct bilirubin, mg/dL	4.0
INR	1.1
Anti-HBs	Positive
IgG anti-HAV	Positive
IgM anti-HAV	Negative
HCV RNA, IU/mL	2.8 million
HCV genotype	1b
IL28B genotype	CC
ANA, U	1.8
SMA	Negative
γ-Globulin, g/dL	1.0

Which of the following should you advise now?

a. Monitor with observation only
b. Prescribe peginterferon
c. Prescribe peginterferon and ribavirin
d. Prescribe peginterferon, ribavirin, and sofosbuvir
e. Perform liver biopsy

VI.12. **A 60-year-old man who originally emigrated from Laos received a diagnosis of chronic HBV infection with cirrhosis 5 years ago. He takes tenofovir to suppress the HBV infection. He has been in a surveillance program for HCC with liver ultrasonography and alpha fetoprotein tests every 6 months. One month ago, surveillance abdominal ultrasonography showed a new 2.5-cm mass in the lateral left lobe of the liver. On confirmatory multiphasic MRI, the mass shows arterial phase enhancement and portal venous and venous phase washout. There is no evidence of portal or hepatic vein involvement or extrahepatic spread. The serum alpha fetoprotein level is 100 ng/mL. The patient has no major comorbidities that would preclude surgery. He has a MELD score of 11. His ECOG performance status is 1. What is the optimal therapy for this patient?**

a. Radiofrequency ablation
b. Percutaneous ethanol injection
c. Orthotopic liver transplant
d. Surgical resection
e. Transarterial chemoembolization

VI.13. **A 45-year-old woman with a 25-year history of mild ulcerative colitis reports a 2-month history of persistent right upper quadrant abdominal discomfort. She is otherwise in good health and has an ECOG performance status of 1. Liver ultrasonography shows a 7-cm mass in the superior right lobe of the liver. MRI performed for further evaluation shows a mass on T1-weighted images that is hypointense with lobular margins and shows minimal enhancement in the arterial phase with progressively increasing enhancement through the venous phase. In addition, the porta hepatis has matted lymph nodes measuring 3×4 cm that are suspicious for metastases. MRCP shows that the peripheral bile ducts have a chain-of-lakes appearance, which suggests previously unrecognized PSC. Percutaneous biopsy of the matted lymph nodes confirms the diagnosis of adenocarcinoma, likely of the upper gastrointestinal tract, with biliary or pancreatic origin. Colonoscopy and EGD are negative. The CA19-9 is 2,550 U/mL. What is the most appropriate management of this patient?**

a. Best supportive care only
b. Orthotopic liver transplant
c. Transarterial chemoembolization
d. Combination chemotherapy with gemcitabine and cisplatin
e. Treatment with the multikinase inhibitor sorafenib

VI.14. **A 30-year-old woman is involved in a motor vehicle accident and sustains a bruise across her abdomen from the seatbelt. Multiphasic CT performed to rule out intra-abdominal injury shows a 6.5-cm homogeneous mass in the inferior right lobe of the liver. The mass shows contrast enhancement in the early arterial phase and a rapid return to isointensity with the rest of the liver in the portal venous phase. The mass appears to have a small central scar. To distinguish between focal nodular hyperplasia and hepatic adenoma, MRI is performed with the contrast agent gadoxetate disodium (Eovist). The mass shows contrast retention on the 20-minute delayed images. No other intra-abdominal pathology is seen. What would be the appropriate next step for this patient?**

a. Biopsy of the mass and immunohistochemical staining for nuclear β-catenin
b. Surgical resection
c. Radiofrequency ablation
d. Conformal external beam radiotherapy
e. No further treatment

VI.15. **A 70-year-old woman with no significant past medical history becomes pruritic, and a week later her husband notices that she has jaundice. Abdominal ultrasonography at the local emergency department showed a large 10-cm cystic lesion located centrally in the liver with through transmission, a distinct far wall, and posterior acoustic enhancement. The lesion stretched and distorted the central bile ducts and there was bilateral peripheral biliary dilatation. A few thin septa were apparent in the lesion without nodularity of the walls or the septa. The radiologist aspirated the cystic lesion and removed 200 mL of clear serous fluid. Cytology and bacterial cultures were negative. After decompression of the cyst, the woman's jaundice began to resolve. What is the optimal method for preventing reaccumulation of this large hepatic cyst and recurrence of jaundice?**

a. Surgical cyst fenestration
b. Laparoscopic cauterization of the cyst lining
c. Partial hepatectomy
d. Percutaneous drainage of the cyst and alcohol instillation
e. Placement of a permanent uncoated metal biliary stent at ERCP

VI.16. A 45-year-old man with a BMI of 35 has mildly elevated ALT levels. Otherwise, he is in good health with no significant comorbidities. Liver ultrasonography shows a heterogeneous 6-cm mass in the inferior right lobe of the liver. MRI performed with gadoxetate disodium (Eovist) shows early intense arterial enhancement of the mass, followed by return to near isointensity in the early portal venous phase. The mass excludes the contrast agent in the 20-minute delayed hepatobiliary phase of the scan. The imaging studies are thought to be most consistent with hepatic adenoma, and a liver biopsy is performed to characterize the adenoma. Histology is consistent with an inflammatory or telangiectatic hepatic adenoma in an otherwise normal liver. Immunohistochemistry for β-catenin shows strong nuclear staining in the mass. What is the optimal management of this patient?

a. Orthotopic liver transplant
b. Surgical resection
c. Follow-up MRI in 6 months
d. No further therapy
e. Radiofrequency ablation

VI.17. A married 35-year-old man is evaluated for elevated levels of transaminases found on a life insurance health screening assessment. He is otherwise healthy and takes no medications other than occasional acetaminophen for headaches. His BMI is normal. He consumes alcohol in moderation (about 2 drinks daily), but he does not smoke or abuse illicit drugs. Laboratory test results are shown below:
Liver ultrasonography shows increased parenchymal echogenicity. Which of the following is the most likely cause of his elevated liver test results?

Component	Result
Hemoglobin, g/dL	14
MCV, fL	102
Platelet count, $\times 10^3/\mu L$	225
INR	1.0
AST, U/L	85
ALT, U/L	45
Total bilirubin, mg/dL	1.0

a. Nonalcoholic fatty liver disease
b. Alcohol-related steatosis
c. Acetaminophen hepatotoxicity
d. Acute hepatitis C
e. Chronic hepatitis C

VI.18. A 45-year-old woman is admitted to the hospital with jaundice and malaise. A diagnosis of alcoholic hepatitis is made and her Maddrey discriminant function is calculated to be 35. Her pulse is 110 beats per minute, and her blood pressure is 110/50 mm Hg. On examination, she has scleral icterus, deep jaundice, and slight asterixis. Laboratory test results are remarkable for a peripheral WBC count of 18,000/μL, INR 2.1, and total bilirubin 35 mg/dL. In addition to abstinence from alcohol, which of the following should be included in the initial management?

a. Prednisolone
b. Prednisolone and pentoxifylline
c. Etanercept
d. Nutritional support without pharmacotherapy
e. Immediate evaluation for liver transplant

VI.19. A 55-year-old widow is referred by her primary physician because she had abnormal liver test results. She has consumed 1 bottle of wine daily for approximately 20 years. Testing for infectious, autoimmune, and metabolic liver diseases has been negative. She is overweight (BMI, 30). On examination, she has spider angiomas and a palpable spleen. Laboratory test results are shown below:

Component	Result
Hemoglobin, g/dL	10
WBC count, /μL	3,000
Platelet count, $\times 10^3/\mu L$	102
INR	1.2
AST, U/L	110
ALT, U/L	60
Total bilirubin, mg/dL	2.9
Albumin, g/dL	3.0

Her calculated MELD score is 12. Which of the following is recommended?

a. Abstinence and a visit with an addiction specialist
b. Acamprosate
c. Liver transplant evaluation
d. Pentoxifylline
e. Weight loss and vitamin E

VI.20. A 60-year-old woman is evaluated for a recent diagnosis of chronic hepatitis C. She has HCV genotype 1a with a high viral load of 10 million copies. Transaminase levels are mildly elevated, and liver biopsy shows mild periportal fibrosis. She has a history of depression and hypothyroidism. She consumes 1 to 2 alcoholic beverages daily. Which of the following should you recommend?

a. Peginterferon and ribavirin
b. Peginterferon, ribavirin, and telaprevir
c. No therapy now
d. Discontinuation of alcohol
e. Another liver biopsy in 1 year

VI.21. A 43-year-old man is in the hospital for fatigue, malaise, icterus, and abnormal liver test results. Three days ago, fever, sore throat, and cough developed, but the symptoms were manageable with over-the-counter acetaminophen and the combination of acetaminophen, dextromethorphan, and doxylamine succinate (NyQuil). His condition worsened yesterday, and he presented to the emergency department. He typically consumes 2 to 3 alcoholic beverages in the evening, but he has not had any since becoming ill. His laboratory evaluation shows INR 2.1, AST 1,240 U/L, ALT 1,021 U/L, and total bilirubin 3.5 mg/dL. What is the most likely explanation of his abnormal liver test results?

a. Alcoholic cirrhosis
b. Alcoholic hepatitis
c. Alcoholic cirrhosis with concomitant alcoholic hepatitis
d. EBV-associated hepatitis
e. DILI

VI.22. A 55-year-old man is evaluated for elevated liver test results. He consumes 2 drinks of alcohol daily. He has mildly elevated transaminases (AST 70 U/L, ALT 25 U/L) and a ferritin level of 350 μg/L, with normal results for a CBC, INR, albumin, and bilirubin. Which of the following is his liver biopsy most likely to show?

a. Cirrhotic nodules
b. Macrovesicular steatosis

c. Hepatocellular iron deposition
d. Ballooning degeneration and Mallory bodies
e. Interface hepatitis with plasma cells

VI.23. A 72-year-old Vietnamese man with a known history of chronic hepatitis B infection presents for the evaluation of abdominal pain, distention, and weight loss. He states that his appetite is poor and he has lost approximately 10 kg in the past several months. On examination, he is cachectic, he has scleral icterus, and ascites is palpable. His liver edge is enlarged and firm. CT of the abdomen with an IV contrast agent shows a large mass in the right lobe of the liver associated with thrombosis of the right and main portal veins. There is patchy enhancement of the thrombus during arterial phase imaging. The serum alpha fetoprotein level is normal at 9 ng/mL. Which of the following should you recommend?

a. Refer for liver transplant
b. Refer for right hepatectomy
c. Refer for portal venography with thrombolytic therapy
d. Begin enoxaparin
e. Refer to hospice

VI.24. A 64-year-old man presents to the emergency department after the acute onset of hematemesis. His past medical history is notable for alcohol-related pancreatitis, for which he was hospitalized 3 years ago. He has remained abstinent from alcohol since that time. In the emergency department, he has postural hypotension. He is obese, but physical examination findings are otherwise unremarkable, and he does not have any stigmata of chronic liver disease. He is resuscitated with fluids, and an emergent upper endoscopy is performed. A large amount of fresh blood and clots are seen within the stomach as well as nonbleeding varices in the gastric fundus. No esophageal varices are seen. Which of the following should you recommend?

a. CT scan of the abdomen with an IV contrast agent
b. Cyanoacrylate glue injection of the gastric varices
c. Transjugular liver biopsy
d. Refer for TIPS placement
e. Refer for liver transplant evaluation

VI.25. A 27-year-old woman presents to the emergency department with gradually progressive abdominal pain and distention over several days. She has no significant medical history and her only medication is an oral contraceptive. On examination, she has obvious abdominal distention with shifting dullness. The liver is enlarged and tender, but splenomegaly is not noted. She denies risk factors for viral hepatitis, alcohol excess, or a family history of liver disease. On ultrasonography, large ascites is noted. Doppler studies confirm patency of the portal and splenic veins. The hepatic veins are not well visualized. Which of the following should you recommend?

a. IV thrombolytic therapy
b. Subcutaneous enoxaparin
c. TIPS placement
d. Hepatic venography
e. Referral for liver transplant

VI.26. A 59-year-old woman is hospitalized for diverticulitis. She has had recurrent episodes of diverticulitis, with the latest episode occurring approximately 6 months ago. On CT of the abdomen, performed as part of her evaluation for sigmoid colectomy, portal vein thrombosis is identified. She has no prior history of thrombotic disorders and is a lifetime nonsmoker. On her most recent imaging, performed 6 months earlier, the portal vein was widely patent. Which of the following should you recommend?

a. TIPS placement
b. Warfarin anticoagulation for 6 months
c. Thrombolytic therapy with IV alteplase
d. Colonoscopy to screen for occult malignancy
e. Bone marrow biopsy

VI.27. A 28-year-old woman underwent living donor liver transplant for cirrhosis secondary to autoimmune hepatitis 6 days ago. Her initial postoperative course has been uneventful and she has been making excellent progress. Her incisional pain is well controlled with low-dose oral opiates. You are contacted by her nurse when the patient has a fever associated with abdominal pain, nausea, and vomiting. On examination, she has a toxic appearance and her condition rapidly deteriorates, with the development of hypotension, tachycardia, and respiratory distress. She is moved to the ICU, where she is resuscitated with IV fluids and blood samples are obtained for cultures. Broad-spectrum antibiotic therapy is started. A chest radiograph is notable for only mild bibasilar atelectasis. Urinalysis results are pending. Laboratory test results are notable for increased AST (>4,000 U/mL) and ALT (>4,000 U/mL), acute kidney injury (creatinine 2.6 mg/dL), and an INR of 3.5. Emergent Doppler ultrasonography of the hepatic allograft shows pneumobilia, a heterogenous parenchymal echotexture, and patent portal and hepatic veins. The hepatic artery is not visualized. Which of the following should you recommend?

a. Thrombolysis with IV alteplase
b. Emergent surgical exploration
c. Listing for retransplant
d. ERCP
e. Bolus IV corticosteroids for acute cellular rejection

VI.28. A 36-year-old man with cirrhosis secondary to PSC presents to the emergency department with massive hematemesis. He is hemodynamically unstable, so he is intubated and admitted to the ICU. He is resuscitated with IV fluids; he is given packed red blood cells, plasma, and platelets; and he receives IV octreotide and ceftriaxone. Urgent upper endoscopy shows large gastric fundic varices with active bleeding. The nearest center with expertise in cyanoacrylate obturation of varices is 6 hours away. Which of the following should you recommend?

a. Band ligation of the bleeding varices
b. Emergent TIPS placement
c. Emergent distal splenorenal shunt surgery
d. Referral for liver transplant evaluation
e. Referral for cyanoacrylate glue injection

VI.29. A 49-year-old man presents to the emergency department because of gross hematemesis that occurred last night. He has a known history of cirrhosis due to chronic hepatitis C and excessive consumption of alcohol. At presentation, he is hemodynamically stable. On examination, he has stigmata of chronic liver disease but no ascites. Laboratory studies show moderate thrombocytopenia (stable from prior values), INR 1.6, and hemoglobin 8.2 g/dL. Upper endoscopy performed in the emergency department shows small esophageal varices without high-risk stigmata and heme staining of the stomach but no evidence of active bleeding. Which of the following should you recommend?

a. Band ligation of the esophageal varices
b. Emergent TIPS placement
c. Nadolol 40 mg by mouth daily at bedtime
d. Referral for liver transplant evaluation
e. Omeprazole 20 mg by mouth twice daily

VI.30. A 52-year-old woman presents to your office for evaluation of fatigue. She has known autoimmune hepatitis with cirrhosis. She has well-compensated cirrhosis (Child-Pugh class A), and her liver function has been stable for several years

with maintenance azathioprine therapy. She has not had ascites, jaundice, or hepatic encephalopathy. On examination, she appears well but fatigued. Laboratory studies show new anemia, and her stool is positive for occult blood. To evaluate the anemia, she undergoes colonoscopy (the findings are unremarkable) and upper endoscopy. In her gastric antrum, there are linear aggregates of erythematous lesions, which bleed on contact and occupy approximately one-third of the circumference of the antrum. The esophagus, duodenum, and proximal stomach (including the gastric fundus) appear normal. Which of the following should you recommend?

a. Biopsy of the gastric mucosal lesions
b. TIPS placement
c. Ferrous sulfate and nadolol
d. Estrogen-containing oral contraceptive
e. Endoscopic argon plasma coagulation

VI.31. A 62-year-old man with cryptogenic cirrhosis returns for routine follow-up. Large (>5 mm diameter) nonbleeding esophageal varices were diagnosed at a screening endoscopy 2 years ago. Nadolol was prescribed for primary prophylaxis. At his follow-up visit, he complains of fatigue, sexual dysfunction, and orthostatic symptoms. He has not had gastrointestinal tract bleeding. His blood pressure (seated) is 105/45 mm Hg, and his pulse rate is 80 beats per minute. Physical examination findings are unchanged from prior visits. There is no evidence of anemia on laboratory assessment. Which of the following should you recommend?

a. Discontinue the nadolol therapy and observe
b. Discontinue the nadolol therapy and begin propranolol
c. Repeat the EGD and discontinue the nadolol therapy if the varices have regressed
d. Discontinue the nadolol therapy and repeat the EGD with band ligation of varices
e. Discontinue the nadolol therapy and refer for TIPS placement

VI.32. A 41-year-old woman is hospitalized for the management of alcoholic hepatitis. She consumes 1 L of vodka every 2 to 3 days and was drinking up to the time of admission. On presentation, she is jaundiced and has muscle wasting and ascites. Her calculated MELD score is 32. A diagnostic paracentesis is performed, and no evidence of spontaneous bacterial pertinonitis is present. Her treatment is methylprednisolone for her alcoholic hepatitis, an alcohol withdrawal protocol, and placement of a nasogastric feeding tube for supplemental feeding. On the third day of hospitalization, she becomes progressively confused and subsequently passes a large melenic stool. She is transferred to the ICU, where she is intubated. IV octreotide therapy is initiated. Emergent EGD shows large varices with stigmata of recent bleeding. In addition to band ligation of the varices, which of the following should you recommend?

a. IV vancomycin
b. IV cefotaxime
c. IV terlipressin
d. IV pantoprazole
e. TIPS placement

VI.33. A 52-year-old white man is found to have elevated liver test results during an insurance physical examination. He has no symptoms and liver tests have not been performed previously. His past medical history is notable for hypertension and arthritis of the right knee. He consumes approximately 2 to 3 alcoholic beverages daily. There is no family history of liver disease. On physical examination, he is overweight (BMI 34) with central body fat distribution. The liver and spleen are not enlarged. Examination findings are otherwise unremarkable. Laboratory test results are shown below:

Component	Result
CBC	Normal
ALT, U/L	52
Total bilirubin, mg/dL	1.0
Glucose (fasting), mg/dL	119
Ferritin, ng/mL	450
Transferrin saturation, %	38
HCV antibody	Negative

Abdominal ultrasonography reveals hepatic steatosis, normal bile ducts, and cholelithiasis without gallbladder thickening. Which is the most likely cause of the abnormal liver test results?

a. *HFE* hemochromatosis
b. Nonalcoholic fatty liver disease
c. Ferroportin disease
d. *TFR2* hemochromatosis
e. HCV infection

VI.34. A 40-year-old white woman presents for evaluation after her older brother received a diagnosis of hemochromatosis-related cirrhosis. She is concerned about liver disease. She is asymptomatic and has no significant medical history aside from migraine headaches. She consumes less than 1 alcoholic beverage weekly. On physical examination, she is a slender woman without findings suggestive of chronic liver disease. Laboratory testing is notable for mild anemia (hemoglobin 10.8 g/dL), normal levels of liver enzymes, transferrin saturation 60%, and serum ferritin 100 ng/mL. *HFE* gene testing reveals 2 abnormal copies of the C282Y mutation. What should you recommend at this time?

a. Perform liver biopsy with iron quantification
b. Perform surveillance ultrasonography every 6 months
c. Begin oral deferasirox
d. Begin therapeutic phlebotomy
e. Recheck iron studies in 2 years

VI.35. A 64-year-old white man presented with abnormal liver test results 5 years ago and received a diagnosis of hemochromatosis. At presentation, his serum ferritin was 1,250 ng/mL, and he began a therapeutic phlebotomy program, which he has tolerated well. Earlier today he presented with gross hematemesis and was hospitalized. Upper endoscopy revealed actively bleeding esophageal varices. After stabilization, transfusion, and band ligation, abdominal ultrasonography was performed and revealed extensive portal vein thrombosis. No mass was seen in the liver, but the hepatic echotexture was coarsened. The serum alpha-fetoprotein level was normal. Which of the following should you recommend?

a. Begin therapeutic anticoagulation
b. Perform contrast-enhanced triple-phase CT of the abdomen
c. Perform a liver biopsy
d. Resume therapeutic phlebotomy at hospital discharge
e. Monitor iron studies and resume phlebotomy when the ferritin level becomes elevated

VI.36. A 49 year-old white man receives a diagnosis of hemochromatosis following routine laboratory testing as part of an insurance physical examination. Genetic testing confirms 2 copies of the C282Y mutation. The patient was adopted, and no family history about his biologic relatives is available. He and his wife inquire about testing for their 5 children, aged 6 to 17. Which of the following should you advise?

a. Defer any testing of children until they are 18 years old
b. Perform *HFE* gene testing for all children now
c. Perform *HFE* gene testing for his wife now

d. Check the children's iron studies now and, if results are normal, annual serum iron studies
e. Check the children's iron studies now and, if results are normal, no further testing

VI.37. A 27-year-old woman is brought to the emergency department by friends after a suicide attempt. The patient was found at home alone. Sometime in the past 48 hours, she ingested a large number of medications, including 40 tablets of 500-mg acetaminophen, along with a large amount of alcohol. At present, she is obtunded and unable to provide a history. Her friends do not know of any family history of liver disease. She is emergently intubated in the emergency department for hypercapnic respiratory failure and admitted to the ICU. Examination in the ICU reveals a sedated woman with multiple tattoos. Her sclerae are icteric. The liver is enlarged, but splenomegaly is not present. No ascites is appreciated. Laboratory test results are markedly abnormal, as shown below:

Component	Result
CBC	Normal
ALT, U/L	7,820
Total bilirubin, mg/dL	3.0
Glucose (fasting), mg/dL	69
INR	2.8
Ceruloplasmin, mg/dL	24
HBV serology	Negative
HCV Antibody	Negative

Which of the following should you recommend?

a. *N*-acetylcysteine
b. D-penicillamine
c. Liver biopsy for hepatic copper quantification
d. Slit-lamp examination
e. A 24-hour urine copper quantification

VI.38. A 52-year-old woman presents for evaluation of elevated serum liver values. After further evaluation and testing, she is found to have a positive serum AMA test. Which of the following serum blood tests should be followed to assess her treatment response?

a. ALT
b. ALP
c. AST
d. Bilirubin
e. Prothrombin time

VI.39. A 60-year-old man with PSC was recently found to have evidence of compensated cirrhosis and portal hypertension on cross-sectional imaging. Which of the following complications is most commonly associated with his current stage of liver disease?

a. Accelerated atherosclerosis
b. Renal insufficiency
c. Nephrolithiasis
d. Seizure disorders
e. Fat-soluble vitamin deficiencies

VI.40. A 30-year-old man presents with new-onset itching and dark urine. Laboratory tests demonstrate elevated serum liver values, including a total bilirubin of 4 mg/dL. Abdominal ultrasonography shows intrahepatic duct dilatation. He is referred for ERCP and found to have changes consistent with PSC. What other tests should be performed at this time?

a. Liver biopsy
b. Intraductal ultrasonography
c. Brush cytology
d. Cholangioscopy
e. Colonoscopy

VI.41. A 42-year-old woman presents with fatigue and elevated serum liver values. Pertinent results are noted for the following: AST 450 U/L, ALT 625 U/L, ALP 300 U/L, and total bilirubin 0.8 mg/dL. Diagnostic testing is positive for ANA, SMA, and AMA. The serum γ-globulin level is 2.8 g/dL. Abdominal ultrasonography findings are unremarkable. Liver biopsy shows moderate portal and lobular infiltrates with lymphocytes and plasma cells and evidence of lymphocytic cholangitis. Which of the following is the most likely diagnosis?

a. Overlap syndrome
b. Small duct PSC
c. AMA-negative PBC
d. Hepatic sarcoidosis
e. Drug-induced autoimmune hepatitis

VI.42. A 38-year-old man with asymptomatic chronic ulcerative pancolitis is found to have an increasing serum ALP level. MRCP shows segmental dilatation of intrahepatic bile ducts in the right and left liver lobes as well as beading of the extrahepatic bile duct. Which of the following statements below is correct?

a. Begin treatment with UDCA
b. Start azathioprine therapy
c. Recommend annual surveillance colonoscopy
d. Recommend annual surveillance colonoscopy at age 40
e. Proceed to liver biopsy

VI.43. A 55-year-old woman presents with painless jaundice. Her total bilirubin is 8 mg/dL. CT of the abdomen shows intrahepatic bile duct dilatation and atypical nodularity involving the entire pancreas. ERCP shows a long, tapering extrahepatic bile duct stricture that requires stent placement. Which of the following tests should be ordered next?

a. Serum AMA
b. Liver biopsy
c. Serum IgG and subclasses
d. Colonoscopy
e. MRCP

VI.44. Which medication is the most common culprit of idiosyncratic DILI?

a. Amoxicillin-clavulanate
b. Acetaminophen
c. Atorvastatin
d. Methotrexate
e. Phenytoin

VI.45. A 34-year-old woman is admitted from the emergency department for recent onset of jaundice and pruritus 4 days ago followed by confusion today. She does not have any history of liver disease. She does not take any prescription medications and does not drink alcohol. She occasionally uses acetaminophen but does not remember the last time she took it. On examination, the patient has scleral icterus, no stigmata of chronic liver disease, a slow response to questions (but with appropriate answers), and no asterixis. Laboratory test results are shown below:

Component	Result
INR	1.8
Total bilirubin, mg/dL	3.2
ALT, U/L	105
AST, U/L	106
ALP, U/L	172
Creatinine, mg/dL	1.2

Results of additional laboratory tests to evaluate possible causes of liver disease, including acetaminophen level, were negative. What is the best treatment option?

a. Prednisone
b. UDCA
c. *N*-acetylcysteine
d. Cholestyramine
e. Phytonadione

VI.46. A 40-year-old man is referred to clinic with elevated aminotransferases (6 times the ULRR) found incidentally during his routine health evaluation. He was previously healthy and does not take prescription medications or over-the-counter supplements, but he does take ibuprofen intermittently. His last ibuprofen dose was about 3 weeks ago. He is asymptomatic now but experienced a few days of malaise, nausea, vomiting, and abdominal pain about 3 weeks ago. He does not consume alcohol or smoke. He is a business executive with occasional domestic travel. He does not have pets. He is a hunter and enjoys eating exotic foods, such as raw pork and deer meat. His BMI is 23. Ultrasonography performed by his primary physician did not show any steatosis or biliary dilatation. Test results were normal for hepatitis A, B, and C; EBV; CMV; ANA; anti–SMA; IgG level; tissue transglutaminase IgG; alpha$_1$-antitrypsin phenotype; iron; and ceruloplasmin. A diagnosis of DILI secondary to ibuprofen has been proposed by a gastroenterology fellow, but you remain skeptical. Which of the following tests would be appropriate in this setting?

a. Rechallenge with ibuprofen
b. Parvovirus
c. Hepatitis E IgM
d. Leptospira serology
e. Creatine kinase

VI.47. A 48-year-old man presents to the outpatient clinic with mild jaundice. His aminotransferase values are just over 1,000 U/L. He consumes 6 to 8 alcoholic drinks (about 100 g of alcohol) daily and recently began taking multiple daily doses (2 g each) of acetaminophen to treat daily headache. What is the mechanism that leads to increased risk of hepatotoxicity in this individual?

a. Alcohol induction of CYP2E1, resulting in increased *N*-acetyl-*p*-benzoquinone imine
b. Increased renal clearance of *N*-acetyl-*p*-benzoquinone imine
c. Increased availability of intrahepatic glutathione
d. Oxidative stress
e. Reduced CYP2E1 activity due to chronic alcohol use

VI.48. Which combination is most likely to lead to the highest risk of acetaminophen hepatotoxicity?

a. Acute alcohol ingestion and normal doses of acetaminophen
b. Chronic alcohol ingestion and normal doses of acetaminophen
c. Chronic alcohol ingestion and multiple supratherapeutic doses of acetaminophen
d. Acute alcohol ingestion and a mildly supratherapeutic dose of acetaminophen
e. No alcohol ingestion and chronic daily use of acetaminophen at normal doses

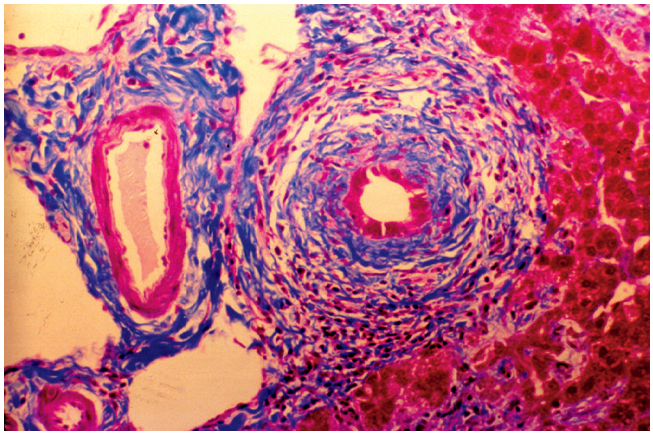
VI.49. A 22-year-old patient presents with valproate hepatotoxicity and significant (grade III) hepatic encephalopathy. What should be the treatment of choice?

a. Antioxidants
b. *N*-acetylcysteine
c. Prednisone
d. UDCA
e. Carnitine

VI.50. A 44-year-old woman presents for evaluation of fatigue and pruritus. She notes xanthelasmas and aphthous oral ulcers for the past 3 to 4 months. Mild hepatomegaly is noted on physical examination. Diagnostic testing for which of the following would be most helpful?

a. Hemoglobin
b. ANA
c. Low-density lipoprotein cholesterol
d. Fasting triglycerides
e. AMA

VI.51. A 24-year-old man presents with a 4-year history of ulcerative colitis that has been stable with mesalamine therapy. He is noted to have abnormal levels of liver enzymes. Laboratory test results include the following: bilirubin 0.9 mg/dL, ALP 305 U/L, ALT 68 U/L, and AST 46 U/L. MRCP findings were normal. Biopsy was performed, and the findings are shown below:



What is the most likely diagnosis?

a. PBC
b. Hepatitis C
c. PSC
d. HCC
e. Autoimmune hepatitis

VI.52. A 57-year-old woman with hypercholesterolemia and a history of atrial fibrillation, for which she takes warfarin, presents because she had abnormal liver test results. Laboratory test results are shown below:

Component	Result
ALP, U/L	380
AST, U/L	67
ALT, U/L	98
GGT, U/L	234
Total bilirubin, mg/dL	3.7
Albumin, g/dL	3.6
INR	2.0
ANA	1:160
AMA	Positive
SMA	1:40
IgG, mg/dL	1,985
IgM, mg/dL	918

What treatment offers delayed progression of this disease to cirrhosis and liver transplant?

a. Prednisone 20 mg daily with tapering doses
b. Ursodiol 7.5 mg/kg daily

c. Cholchicine 6 mg daily
d. Pentoxyfilline 400 mg twice daily
e. Ursodiol 13 to 15 mg/kg daily

VI.53. A 28-year-old previously healthy woman presents with a 3-week history of fatigue, shortness of breath, and right upper quadrant pain. She has mild scleral icterus and tender hepatomegaly on physical examination. Laboratory test results are shown below:

Component	Result
ALT, U/L	367
AST, U/L	237
ALP, U/L	187
Total bilirubin, mg/dL	4.5
INR	1.2
Albumin, g/dL	3.6
Ferritin, ng/mL	888
AMA	Negative
ANA	1:1,280
SMA	1:320
IgG, mg/dL	7,100

Biopsy findings included only a few portal tracts, but all had lymphoplasmacytic infiltrate with interface hepatitis and mild cholangitis. What is the best next step?

a. ERCP
b. Phlebotomy
c. Steroid-based treatment
d. Ursodiol
e. Transplant evaluation

VI.54. If the 28-year-old patient in the previous question receives treatment, what is the likelihood of remission with steroid therapy with or without azathioprine therapy?

a. 100% by 1 year
b. 20% to 25% by 1 year
c. 50% to 55% by 3 years
d. 80% to 85% by 3 years
e. 10% without azathioprine

VI.55. Which of the following histologic features best distinguishes NASH from ASH on histology?

a. Mallory bodies
b. Hepatocyte balloon degeneration
c. Apoptotic bodies
d. Steatosis
e. None of the above

VI.56. A 42-year-old man presents for a routine evaluation. He is asymptomatic, physical examination findings are normal, he takes no medications, and he has no family history of liver disease. He is not sexually active, and he denies IV or intranasal drug use, recent travel, and blood transfusions. Laboratory test results include the following: AST 85 U/L, ALT 43 U/L, and GGT 147 U/L; ALP, total bilirubin, and MCV were all within the reference range. He admits to drinking 10 to 12 drinks daily in the past 4 weeks since losing his job. Ultrasonography shows fatty liver. Approximately what percentages of patients with alcoholic fatty liver will progress to more advanced liver disease with either abstinence or continued excess drinking?

a. With abstinence, 0%; with continued excess drinking, 20%
b. With abstinence, 0%; with continued excess drinking, 50%
c. With abstinence, 10%; with continued excess drinking, 60%
d. With abstinence, 5%; with continued excess drinking, 20%
e. None of the above

VI.57. A 46-year-old man presents with fatigue, dark urine, and abdominal swelling. He admits to drinking a few beers daily since his teen years, but he has not had significant prior medical problems. He has been drinking more heavily since he has been unemployed (3-4 months). He denies blood transfusions and IV drug use. On physical examination, he has tachycardia and low-grade fever. Scleral icterus is prominent. Abdominal examination reveals shifting dullness. The liver span is increased on percussion. You diagnose acute alcoholic hepatitis. Which clinical or laboratory feature would be *least* predictive of the patient's survival?

a. Bilirubin level
b. Prothrombin time
c. Albumin level
d. Hepatic encephalopathy
e. Creatinine level

VI.58. A 52-year-old alcoholic man comes to the clinic complaining of back pain for 8 weeks and jaundice for 3 days. He is hemodynamically stable. Laboratory test results include the following: AST 6,145 U/L, ALT 5,090 U/L, total bilirubin 4.6 mg/dL, and INR 2.3. Which of the following is the most likely diagnosis?

a. Alcoholic hepatitis
b. Acetaminophen toxicity
c. Acute hepatitis A
d. Shock liver
e. Choledocholithiasis

VI.59. A 49-year-old woman with abnormal liver test results is referred for evaluation. She has been treated for high cholesterol with simvastatin for 1 year. After her simvastatin was withheld for 1 month, her liver tests were repeated, but the results were unchanged. She is otherwise healthy. Laboratory test results are shown below:

Component	Result
ALT, U/L	122
AST, U/L	87
Total bilirubin, mg/dL	0.7
ALP, U/L	146
INR	0.8
Blood pressure, mm Hg	142/88
Heart rate, beats per minute	78
BMI	36
HBsAg	Negative
Anti-HCV	Negative
ANA	1:160
SMA	Negative
AMA	Negative
IgG, mg/dL	350
Ferritin, ng/mL	360
Iron saturation, %	36

Ultrasonography shows fatty liver with no masses. What should be the first-line treatment of this patient?

a. Start prednisone 30 mg daily with azathioprine 50 mg daily
b. Start prednisone 60 mg daily
c. Discontinue simvastatin permanently
d. Recommend weight loss of 10% excess body weight and resume simvastatin if indicated by the cholesterol status
e. Start pioglitazone 10 mg and vitamin E 400 international units daily

VI.60. A 26-year-old woman presents with jaundice in her 16th week of pregnancy. She has a 2-year-old child from a prior pregnancy, which was uneventful. The patient complains of fatigue, nausea, and malaise. She takes no medications except for a

prenatal multivitamin. The patient does not drink alcohol and has not travelled outside the United States. She does not have any ill household contacts, and her 2-year-old child has not been absent from day care because of illness. Laboratory test results include the following: CBC normal, AST 1,800 U/L, ALT 2,200 U/L, ALP 200 U/L, total bilirubin 3.6 mg/dL, and INR 1.1. Which of the following is the most likely diagnosis?

a. Acute fatty liver of pregnancy
b. Acute Budd-Chiari syndrome
c. Acute hepatitis A
d. ICP
e. HELLP syndrome

VI.61. A 31-year-old woman presents for progressive abdominal pain and distention with nausea over the past 2 weeks. Her symptoms began several days postpartum following her first pregnancy, and she had initially attributed them to her difficult delivery. She had a prolonged labor and required forceps delivery of the baby. Her past medical history is notable for deep vein thrombosis several years ago, which was attributed to her use of oral contraceptives at that time. On examination she has palpable ascites, her liver is enlarged, and venous collaterals are visible on her abdominal wall. Which of the following is the most likely diagnosis?

a. Acute fatty liver of pregnancy
b. Acute Budd-Chiari syndrome
c. Hyperemesis gravidarum
d. ICP
e. HELLP syndrome

VI.62. A 19-year-old woman presents for evaluation because she is concerned that she has an allergy. She is 29 weeks into her first pregnancy and has had worsening diffuse itching over the past several weeks. She does not have a rash. Her past medical history is unremarkable, but she does have a family history of gallstones. On examination she is noted to have excoriations but no rash. No jaundice is present. Laboratory test results include the following: CBC normal, AST 300 U/L, ALT 420 U/L, ALP 340 U/L, total bilirubin 2.6 mg/dL, and INR 0.9. Ultrasonography of the abdomen shows cholelithiasis, but the bile ducts appear normal. Which of the following should be recommended?

a. Induce delivery immediately
b. Begin corticosteroid therapy followed by induction of delivery
c. Perform ERCP
d. Perform laparoscopic cholecystectomy
e. Begin UDCA therapy

VI.63. A 22-year-old woman underwent liver transplant 1 year ago because of acute liver failure from DILI (trimethoprim-sulfamethoxazole). She has been incompletely adherent to her posttransplant medications and has had 2 episodes of acute cellular rejection requiring treatment with corticosteroids. Her current medications include low-dose aspirin, tacrolimus, and mycophenolate mofetil. She recently married and now seeks counselling regarding pregnancy. Which of the following statements is most correct?

a. Pregnancy is contraindicated following liver transplant, and the patient should undergo surgical contraception (sterilization)
b. Pregnancy would be associated with an increased risk of recurrent acute liver failure
c. Her immunosuppressive medication regimen does not contain drugs with known teratogenicity
d. Pregnancy would be associated with an increased risk of chronic rejection
e. Pregnancy is safest in transplant recipients beyond the first 2 years after transplant

VI.64. A 32-year-old woman is 30 weeks pregnant with twins. This is her first pregnancy. She had difficulty conceiving and ultimately underwent in vitro fertilization. She is brought to the emergency department by her husband who found her confused at home. She has been unwell for several days with "the flu," which developed after she travelled to Texas to visit relatives last week. Her husband reports that the patient has had anorexia, malaise, and nausea with vomiting. She has been taking over-the-counter cold medication as directed on the label in addition to her prenatal multivitamin. On examination the patient is disoriented with a flapping tremor. Her sclera are icteric. She is hypertensive and has pitting lower extremity edema (2+). Laboratory test results include the following: WBC count elevated, platelet count normal, AST 310 U/L, ALT 280 U/L, ALP 200 U/L, total bilirubin 4.1 mg/dL, INR 2.6, and creatinine 3.2 mg/dL. Which of the following is the most likely diagnosis?

a. Acute fatty liver of pregnancy
b. Acute Budd-Chiari syndrome
c. Acute hepatitis A
d. DILI
e. HELLP syndrome

VI.65. A 54-year-old woman with cirrhosis secondary to NASH is found to have liver masses during surveillance ultrasonography. Her liver disease has otherwise been well compensated. A screening upper endoscopy performed 1 year ago showed small (<5 mm diameter) nonbleeding esophageal varices. Contrast-enhanced CT performed because of the abnormal ultrasonographic findings showed 2 liver masses: a 3.5-cm-diameter mass in the superior right lobe and a 2.2-cm mass in the inferior right lobe. Both lesions demonstrated arterial enhancement and were hypointense on portal venous phase imaging. There was no evidence of extrahepatic spread. Her serum alpha-fetoprotein level is not elevated. Which of the following should you recommend?

a. Liver transplant evaluation
b. Surgical consultation for right hepatectomy
c. Transarterial chemoembolization
d. Ultrasound-guided biopsy
e. Hospice referral

VI.66. A 48-year-old man has long-standing PSC. He presents with jaundice, progressive fatigue, and refractory pruritus. He has had to reduce his hours at work from full-time to part-time because of the symptoms of his liver disease. His history is notable for a total proctocolectomy 25 years ago for refractory ulcerative colitis and nonbleeding esophageal varices treated with endoscopic band ligation 1 year ago. A recent MRCP reveals diffuse biliary stricturing without a dominant stricture and no worrisome liver masses. His calculated MELD score is currently 14. He inquires about liver transplant. The average MELD score for transplant in the region is 28. Which of the following statements is most correct?

a. He should wait for deceased donor liver transplant
b. He should be evaluated for living donor liver transplant
c. Liver transplant is contraindicated because of the risk of cholangiocarcinoma
d. Living donor liver transplant is contraindicated because of his prior abdominal surgery
e. Living donor liver transplant is contraindicated because of the lack of survival benefit for patients with low MELD scores

VI.67. A 42-year-old woman underwent deceased donor transplant for PSC 9 weeks ago. Her postoperative course was notable for mild acute cellular rejection at day 7, which was treated with bolus corticosteroid therapy. Otherwise, she has been doing well and has adhered to her posttransplant immunosuppressive therapy. She returned to the clinic because she has had progressive pruritus over the past few days. When

she awoke this morning she noticed scleral icterus. She denies fever or abdominal pain. She is very worried that her "PSC has come back." Laboratory test results are notable for elevated levels of ALP (600 U/mL) and total bilirubin (3 mg/dL) and mild elevations of AST and ALT (<2 times the ULRR). Ultrasonography reveals normal-appearing hepatic parenchyma; normal flow in the hepatic artery, portal veins, and hepatic veins; and nondilated intrahepatic bile ducts. Which is the most likely cause of the patient's symptoms?

a. Anastomotic biliary stricture
b. Ischemic biliary stricture
c. Recurrent PSC
d. Acute cellular rejection
e. Ascending cholangitis

VI.68. A 52-year-old woman presents for evaluation of fever 7 months following living donor liver transplant for PBC. The donor was her 24-year-old son. Her postoperative course was notable for steroid-resistant acute cellular rejection, which required treatment with antithymocyte globulin during the first week following transplant. Fever, malaise, nausea, vomiting, and profuse diarrhea have developed over the past 24 hours. On examination she looks ill but is hemodynamically stable. Her mucous membranes are dry. She does not have jaundice or a rash. She has generalized mild abdominal tenderness, but no rebound or guarding is noted. Her transplant incision is well healed. Laboratory test results include the following: WBC count 1,900/μL, hemoglobin 11.2 g/dL, ALP 168 U/L, AST 119 U/L, ALT 132 U/L, total bilirubin 0.9 mg/dL, and creatinine 2.9 mg/dL. Which of the following is the most likely cause of the patient's clinical syndrome?

a. Bile leak
b. CMV gastroenteritis
c. Recurrent acute cellular rejection
d. Anastomotic biliary stricture
e. *Clostridium difficile* enterocolitis

VI.69. Which of the following patients is *not* a potential candidate for liver transplant?

a. A 62-year-old woman with PBC complicated by portopulmonary hypertension
b. A 29-year-old man with noncirrhotic PSC complicated by a hilar cholangiocarcinoma
c. A 48-year-old woman with a solitary liver metastasis from a sigmoid colon carcinoma
d. A 24-year-old man with renal failure from primary hyperoxaluria
e. A 58-year-old woman with peripheral neuropathy from familial amyloidosis

Answers

VI.1. Answer c.
This patient presents with a chronic indeterminate cholestatic liver disease, and liver biopsy would be advised to assess for AMA-negative PBC or an infiltrative disorder such as sarcoidosis. LKM1 autoantibodies are a feature of type 2 autoimmune hepatitis, which would be a consideration if the liver test elevations were hepatocellular as opposed to cholestatic. ERCP should be done if there is suspicion of biliary obstruction; the absence of bile duct dilatation on CT makes biliary obstruction less likely. Weight loss with serial monitoring of liver test results would be an option in nonalcoholic fatty liver disease, which is usually also characterized by more prominent hepatocellular enzyme elevations. Ursodiol would not be recommended unless the diagnosis was PBC.

VI.2. Answer c.
The presence of fever, mental status changes with imaging changes of encephalitis, and very high aminotransferase levels are consistent with herpes hepatitis, and acyclovir should be initiated immediately. About 30% of patients with herpes encephalitis do not have a skin rash. Wilson disease would be rare in a patient of this age, and aminotransferases do not reach this level in Wilson disease. Patients with ischemic liver injury often present with very high aminotransferase levels but usually after a hypotensive episode. Acetaminophen also produces very high aminotransferases but would not account for the fever. Liver injury from a drug or toxin other than acetaminophen does not cause aminotransferase elevation to this degree.

VI.3. Answer d.
The patient has mild steatohepatitis, confirmed on biopsy 2 years ago. ALT increases mildly in up to 30% of patients after initiating lipid-lowering agents; these increases are rarely progressive and observation is advised. An HCV RNA test is not necessary given that the anti-HCV test was negative and there are no features of acute hepatitis. MRCP would be helpful if this were a cholestatic liver injury. Liver biopsy is not necessary since it is unlikely that there has been a progression of liver disease over a short interval. Discontinuation of simvastatin would be premature.

VI.4. Answer d.
This patient has a cholestatic liver disease with liver biopsy findings consistent with primary biliary disease. About 10% of patients with PBC have negative tests for AMA, and many of these patients have positive tests for ANA and SMA. Ursodiol is effective for both AMA-negative and AMA-positive PBC and should be given to this patient. MRCP and ERCP would be indicated if either the biopsy or the ultrasonography suggested a large-duct obstruction. Prednisone and azathioprine would be used for autoimmune hepatitis, which would be suggested by a predominant hepatocellular injury with a plasma cell portal infiltrate with interface and lobular activity. A further period of observation without treatment would not be recommended since a diagnosis with a proven therapy has already been established.

VI.5. Answer c.
The patient has cirrhosis, and in a young patient, Wilson disease needs to be excluded. Since liver tissue is already available, the easiest and most definitive test would be determination of hepatic copper concentration. Some patients with Wilson disease have a ceruloplasmin level in the low end of the reference range. EBV infection might explain the episode that occurred 16 weeks ago but would not explain the cirrhosis, so EBV serologic and heterophile antibody tests would not be helpful. Autoimmune hepatitis would be less likely because the aminotransferase elevations were only modest and the γ-globulin level was normal. A mild elevation of ANA is a nonspecific finding. Vitamin E might be helpful for nonalcoholic fatty liver disease in the absence of other risk factors, but the finding of mild steatosis in a patient without risk factors such as obesity or diabetes mellitus is suggestive of another cause, such as Wilson disease, hepatitis C, drugs, or celiac disease.

VI.6. Answer b.
The patient has fever and granulomas in the liver, which suggest an infectious cause. The clue to the diagnosis is the administration of intravesical BCG 3 months ago; this can rarely lead to systemic infection due to *Mycobacterium bovis*. Tuberculosis is less likely in the absence of exposure. Granulomatous hepatitis

overlaps with sarcoidosis but is largely a diagnosis of exclusion. Q fever produces granulomas in the liver but rarely cause symptoms for this long in the absence of a history of immune compromise. PBC is a cholestatic disease with ill-defined granulomas of the portal tract. PBC would not explain the fever or the multiple lobular granulomas.

VI.7. Answer a.
In a young patient who likely acquired hepatitis B at birth, the presence of a normal ALT level, positive HBeAg, and a very high HBV DNA level is consistent with the inactive carrier state, and serial monitoring of ALT would be advised. Patients in the inactive carrier state should be monitored with serial determinations of ALT to assess for conversion to HBeAg-positive chronic hepatitis B. Performing liver ultrasonography and monitoring alpha fetoprotein levels for surveillance for HCC is advised for hepatitis B patients with cirrhosis, Asian men older than 40 years, Asian women older than 50 years, African patients older than 20 years, patients with a family history of HCC, and perhaps those with persistent elevation of ALT and high levels of HBV DNA. This patient does not meet any of those criteria, so HCC surveillance would not be advised.

VI.8. Answer d.
Normal results for ALT and anti-HBe and an HBV DNA level less than 10^4 IU/mL are consistent with an inactive carrier state. Even though treatment of hepatitis B would not be advised, African patients with hepatitis B have a high enough risk of HCC that surveillance is advised in those older than 20 years. Patients in the inactive carrier state generally do not require liver biopsy.

VI.9. Answer a.
Hepatitis B treatment is advised for patients with decompensated cirrhosis who have any detectable HBV DNA. Tenofovir or entecavir would be the agents of choice; peginterferon would be contraindicated for someone with decompensated cirrhosis because of the risk of precipitating a flare of hepatitis. Liver biopsy is not necessary given the other clinical evidence consistent with cirrhosis. A TIPS would not be recommended in the patient, who appears to have had control of variceal bleeding with endoscopic therapy. Ultrasonography would not be needed since CT was already performed; ultrasonography for surveillance of HCC could be considered 6 months later.

VI.10. Answer c.
Patients with hepatitis C occasionally present with symptoms of cryoglobulinemia. Patients with mild manifestations of cryoglobulinemia, such as rash or proteinuria, can be treated with hepatitis C therapy. Those with severe systemic manifestations of cryoglobulinemia, such as renal failure, are generally treated initially with rituximab-based immunosuppressive therapy, and hepatitis C therapy is considered later.

VI.11. Answer a.
This patient presented with an acute hepatitis and hepatitis C. The time course of her risk factor for hepatitis C is consistent with recent acquisition of the virus. Patients with acute hepatitis C, especially those with IL28B genotype CC, who have a higher chance of clearance than those with IL28B genotype TT or CT, can be monitored for 3 months to provide an opportunity for spontaneous resolution of the infection. If HCV RNA persists beyond that point, treatment would be advised. Given the recent acquisition of infection, liver biopsy would not help in management and therefore would not be recommended.

VI.12. Answer c.
The imaging features are diagnostic of a new HCC: arterial enhancement and portal venous washout in a new liver mass occurring with liver cirrhosis in a patient with chronic HBV infection under surveillance for HCC. The mass fits the Milan criteria, and there is no evidence of macrovascular invasion or distant metastases. Although radiofrequency ablation or percutaneous ethanol injection would be considered if this patient had comorbidities that precluded surgery, orthotopic liver transplant is the preferred option for this patient because it addresses both the HCC and the cirrhosis. With a MELD score greater than 9, this patient has a high risk of liver decompensation after surgical resection; hence, resection is not the best option. Transarterial chemoembolization may be used to treat the tumor while awaiting liver transplant but is not the optimal therapy by itself for this patient who is eligible for potentially curative treatment.

VI.13. Answer d.
The scenario describes a patient with ulcerative colitis and previously unrecognized PSC who is at risk of cholangiocarcinoma. The imaging and histologic features are consistent with intrahepatic cholangiocarcinoma. The relatively large extrahepatic lymph node involvement and the high CA19-9 all support the presence of significant metastatic disease. The patient therefore has advanced-stage intrahepatic cholangiocarcinoma and is best treated with the combination of gemcitabine and cisplatin. Given the patient's good performance status, best supportive care only is not indicated. Results are poor for orthotopic liver transplant in patients with intrahepatic cholangiocarcinoma. Transarterial chemoembolization is inappropriate since it would not address the extrahepatic disease. Sorafenib is not approved for first-line therapy of advanced intrahepatic cholangiocarcinoma.

VI.14. Answer e.
This incidentally discovered liver mass in a young woman has typical features of focal nodular hyperplasia, with rapid homogeneous enhancement in the arterial phase, return to isointensity in the portal venous phase, the presence of a central scar, and contrast retention in the delayed hepatobiliary phase. Focal nodular hyperplasias are benign polyclonal growths in the liver thought to develop around a vascular malformation. Focal nodular hyperplasias do not require treatment unless they cause pain. Immunohistochemistry for β-catenin is indicated for determining whether hepatic adenomas are at risk for malignant transformation; it is not indicated for focal nodular hyperplasia. Surgical resection is indicated only for symptomatic patients. Radiofrequency ablation and conformal radiotherapy are not indicated.

VI.15. Answer d.
This patient presents with a large hepatic cyst that is compromising biliary flow. There is no evidence of infection or malignancy. The most cost-effective initial approach is percutaneous drainage and alcohol instillation to attempt to ablate the cyst. If this approach is unsuccessful, surgical cyst fenestration would be indicated. There is no role for laparoscopic cauterization or partial hepatectomy. Placement of a permanent biliary stent is not appropriate for this benign condition.

VI.16. Answer b.
Surgical resection is most appropriate for the β-catenin–activated inflammatory hepatocellular adenoma described here, which carries a risk of malignant transformation. Since the surrounding liver is normal, liver transplant is not indicated. Repeating the

MRI in 6 months will not change the indication for surgery, and no further therapy is not an appropriate response. The lesion is too large for effective radiofrequency ablation.

VI.17. Answer b.
The most likely diagnosis is alcohol-related steatosis. Clues to the diagnosis include moderate alcohol use, elevated MCV, high AST:ALT ratio, and normal BMI. Fatty liver disease is another cause of steatosis but is less likely without other features of the metabolic syndrome. While this patient should avoid acetaminophen because of his alcohol use, a patient with acetaminophen hepatotoxicity would typically present with higher levels of transaminases and liver synthetic function abnormalities. Acute hepatitis also generally produces higher levels of liver enzymes and often jaundice. Chronic hepatitis C could produce this clinical picture but is less likely given this patient's lack of specific risk factors.

VI.18. Answer a.
The patient's Maddrey discriminant function is greater than 32, suggesting a benefit with use of either corticosteroids or pentoxifylline, although there are no clear data on the use of these agents together. Etanercept has not been proved to be effective in this clinical setting. Nutritional support would be indicated but in conjunction with pharmacotherapy. Liver transplant could be considered if the patient does not have a response to medical management, as assessed by a decrease in bilirubin levels and the calculated Lille score after 7 days.

VI.19. Answer a.
This patient has alcohol-related cirrhosis. The key intervention is abstinence and management of alcoholism. Acamprosate may have a role in refractory alcoholism but should be considered only with an experienced addiction psychiatrist. Her low MELD score suggests that the risks of liver transplant would currently outweigh the benefit. Pentoxifylline has no role in the management of alcoholic cirrhosis. While the patient is overweight and may benefit from weight loss, this is not as critical as discontinuation of alcohol. Vitamin E may have some role in nonalcoholic fatty liver but is not recommended for alcoholic liver disease.

VI.20. Answer d.
Patients with chronic hepatitis C should not consume alcohol because synergistic liver damage can occur. This patient has some relative contraindications to interferon-based therapy, and since she has only minimal fibrosis, there is no urgency for treatment. Another liver biopsy is unlikely to show significant changes after 1 year.

VI.21. Answer e.
The most likely explanation of the patient's syndrome is acetaminophen hepatotoxicity. Chronic alcohol use induces the CYP 2E1 isozyme, which lowers the threshold for acetaminophen hepatotoxicity. Discontinuation of alcohol further drives acetaminophen toward its toxic metabolites. This patient was using multiple acetaminophen-containing products and does not have features of advanced alcohol-related liver disease or EBV hepatitis.

VI.22. Answer b.
This patient most likely has alcohol-related steatosis. Since he has normal liver synthetic function, established cirrhosis is unlikely. Mildly elevated ferritin may be present with chronic alcohol use but does not suggest hereditary hemochromatosis. Ballooning degeneration and Mallory bodies are features of alcoholic hepatitis, which he does not have. Interface hepatitis with plasma cells would be seen in autoimmune hepatitis, which is less likely in this patient.

VI.23. Answer e.
This patient with chronic hepatitis B infection has HCC. The normal alpha-fetoprotein level should not dissuade you from the diagnosis, particularly in this high-risk patient. The portal vein thrombosis is due to tumor thrombus, as evidenced by arterial enhancement of the clot. Unfortunately, symptomatic HCC carries a grave prognosis with a median survival of approximately 2 to 3 months. Tumor thrombosis is by definition extrahepatic spread of the malignancy, so neither hepatectomy nor transplant is indicated. Anticoagulation or thrombolytic therapy does not have a role in the management of tumor thrombosis.

VI.24. Answer a.
When isolated gastric fundal varices are found, they should raise the possibility of sinistral hypertension from splenic vein thrombosis, especially in the absence of known liver disease. With a prior episode of pancreatitis, this patient has a risk factor for splenic vein thrombosis. Contrast-enhanced CT would document the presence of splenic vein thrombosis; if it were present, the treatment of choice would be splenectomy. TIPS placement would be indicated for gastric variceal hemorrhage due to cirrhosis.

VI.25. Answer b.
This patient presents with ascites due to Budd-Chiari syndrome. Although the symptoms are recent, the acuity of the thrombosis is unknown. Hepatic venography would confirm the diagnosis, but the diagnosis is fairly secure according to the constellation of clinical findings and the lack of visualization of the hepatic veins on Doppler ultrasonography. She does not have evidence of liver failure and medical management has not failed, so TIPS and transplant are not treatments of choice at this time. The most appropriate therapy is anticoagulation and diuretic therapy. Thrombolytic therapy is used in acute hepatic vein thrombosis and should be delivered by catheter-directed therapy rather than by systemic dosing.

VI.26. Answer b.
This patient has acute portal vein thrombosis. The acute inflammatory state due to her diverticulitis is the precipitating factor. Patients with acute portal vein thrombosis should receive anticoagulation therapy to prevent progression of thrombosis and the development of portal hypertension. In the presence of an intra-abdominal inflammatory process, a bone marrow examination for hematologic disorders is not necessary. Systemic thrombolytic therapy is also not recommended in the absence of acute hepatic decompensation. Colonoscopy is relatively contraindicated in the presence of acute diverticulitis.

VI.27. Answer c.
This patient has acute HAT following transplant and severe ischemic necrosis with graft dysfunction. Patients who undergo living donor liver transplant are at increased risk of HAT because of the smaller vessels and the need for arterial reconstruction. When HAT and severe graft dysfunction develop within 7 days of transplant, the patient should be listed for retransplant with a high priority for organ allocation (similar to patients with acute liver failure). Systemic thrombolysis is contraindicated in the presence of severe coagulopathy. Pneumobilia is due to biliary ischemia and necrosis, and the use of instruments in the bile ducts for ERCP is contraindicated. While acute cellular

rejection is a common cause of elevated aminotransferases in the early posttransplant period, the severity of the clinical scenario and the sonographic evidence of HAT argue against that diagnosis.

VI.28. Answer b.
This patient has hemorrhagic shock from actively bleeding gastric varices. While cyanoacrylate glue injection is a reasonable therapeutic approach (although this is an off-label use of cyanoacrylate glue in the United States), the expertise is not available locally and the patient's condition is likely not stable enough for the long-distance transfer that would be required. TIPS placement would be the most appropriate therapy. Band ligation is not effective for large fundic varices (because of the submucosal location of the varices). Surgical expertise for splenorenal shunting typically requires transfer to a tertiary referral center and is best suited for nonemergent situations. While this patient will ultimately benefit from transplant, controlling the active hemorrhage requires emergent treatment.

VI.29. Answer a.
This patient with known cirrhosis presented with an acute upper gastrointestinal tract hemorrhage. The bleeding should be presumed to be variceal until proved otherwise. Small esophageal varices were noted on examination, and there was evidence of recent bleeding (heme staining in the stomach). Since no other bleeding lesions were identified, the varices are the likely source and should be treated endoscopically to prevent rebleeding. While nonselective β-blockade would be appropriate as part of long-term secondary prophylaxis, it does not replace endoscopic therapy, particularly in an acute bleeding episode. TIPS should be reserved for recurrent or refractory bleeding. This patient will ultimately benefit from transplant, but controlling the active hemorrhage requires emergent treatment.

VI.30. Answer e.
This patient presents with chronic gastrointestinal tract bleeding in the presence of cirrhosis. The endoscopic findings are consistent with GAVE, often known as watermelon stomach. GAVE may be amenable to endoscopic coagulation when it is limited in distribution, as in this patient. Mucosal biopsy can be helpful in distinguishing GAVE from portal hypertensive gastropathy when the endoscopic appearance is not clear, which is not the case in this patient. Treatment with β-blockade and iron supplementation and TIPS placement are of benefit in patients with chronic bleeding from portal hypertensive gastropathy, which is typically not amenable to endoscopic therapy. Estrogen therapy can be considered for GAVE but would typically be used in patients with diffuse ectasia not amenable to endoscopic therapy.

VI.31. Answer d.
This patient is having unacceptable adverse effects from the β-blocker therapy being used as primary prophylaxis. Given his large varices, his therapy should be changed to an alternate form of primary prophylaxis—in this case, band ligation. Dose reduction may improve his symptoms, but the β-blockade would likely be inadequate to prevent variceal hemorrhage (goal heart rate, about 60 beats per minute). TIPS placement does not have a role in the primary prophylaxis of variceal bleeding.

VI.32. Answer b.
Antibiotic therapy confers survival benefit for patients with cirrhosis and acute gastrointestinal tract bleeding. The most common causes of infection in patients with cirrhosis are enteric gram-negative bacilli, and antibiotic coverage should target these organisms. Therefore, vancomycin would be an inappropriate choice. While oral norfloxacin is typically recommended, oral medications may be difficult to use in the presence of acute upper gastrointestinal tract hemorrhage and hematemesis. Patients should also be treated with vasoactive medications such as octreotide. Terlipressin could be used for management of variceal hemorrhage, but it is not approved by the FDA. TIPS placement should be reserved for patients with refractory or recurrent variceal bleeding. While some recent studies suggest that there may be a survival benefit with early TIPS placement for variceal hemorrhage, this finding needs to be confirmed with other studies before becoming widely accepted.

VI.33. Answer b.
This is a common clinical scenario. The patient's transferrin saturation is not elevated, which would typically be seen in hemochromatosis. This patient has multiple features of the metabolic syndrome (obesity, hypertension, and impaired fasting glucose) and evidence of hepatic steatosis. Elevations in ferritin occur with other forms of liver disease since ferritin is an acute phase reactant. While the presentation of ferroportin disease does include elevated ferritin and a low to normal transferrin saturation, the clinical features are much more in keeping with fatty liver disease, which is a common entity.

VI.34. Answer e.
While this young woman has the typical hemochromatosis gene mutation, she does not have any clinical or laboratory evidence of iron overload. Iron overload develops less often and later in women than in men because of reproductive blood loss. This patient does not require therapy at this time. She should be observed since progressive iron overload may develop, and she should begin therapeutic phlebotomy when her serum ferritin level is abnormally elevated. Liver biopsy is invasive and unlikely to provide additional useful information in this case. Surveillance for HCC is needed only for cirrhotic patients who have hemochromatosis. Oral iron chelators are most commonly used in patients with secondary iron overload due to blood dyscrasias.

VI.35. Answer b.
This patient was likely to have had cirrhotic-stage hemochromatosis at his initial presentation. Patients with cirrhotic hemochromatosis are at greatly increased risk for HCC. If a patient has a clinically significant portal vein thrombosis, tumor thrombus must be excluded. While ultrasonography did not reveal a mass, a high degree of awareness must be maintained, and contrast-enhanced imaging (CT or MRI) is appropriate. The negative predictive value of alpha fetoprotein is insufficient to exclude HCC.

VI.36. Answer c.
Since hemochromatosis follows a mendelian pattern of inheritance, all the children will inherit 1 mutant *HFE* copy from their father. As a practical matter, genetic testing of the mother is the simplest next step. If she is not a carrier of a mutant *HFE* gene, the children will only be carriers themselves and not be at risk for iron overload states.

VI.37. Answer a.
The clinical scenario is most consistent with acetaminophen-related hepatotoxicity. Ceruloplasmin, an acute phase reactant, is often modestly depressed with severe acute hepatic injury.

VI.38. Answer b.
ALP is the most sensitive and specific indicator of response to ursodiol therapy, and various cutoff values have been used to indicate a response. Improvement in aminotransferase levels can occur but is less predictive of response than the ALP level. Increases in bilirubin level and prothrombin time indicate advanced disease and generally do not improve with ursodiol therapy.

VI.39. Answer e.
In patients with cirrhosis from cholestatic liver disease, fat-soluble vitamin deficiencies develop because of the advanced state of liver disease. Patients with PSC may have hyperlipidemia but do not seem to have an increased risk of atherosclerosis. Nephrolithiasis can develop in patients with PBC rather than PSC. Renal function is not disturbed with compensated cirrhosis, and the development of seizure disorders is unrelated to cholestatic liver disease.

VI.40. Answer c.
Given the symptoms at initial presentation and the new diagnosis of PSC, this patient is at increased risk for ductal cholangiocarcinoma. Since ductal cholangiocarcinoma can appear as a benign stricture on ERCP, it is mandatory that brush cytology be evaluated to rule out cancer. Intraductal ultrasonography and cholangioscopy are additional tests that can be performed if cytology is equivocal for malignancy. While colonoscopy is important to perform for excluding IBD, it is not the next test that needs to be done for this patient. Given the findings on ERCP, a liver biopsy is not required for confirmation of the diagnosis of PSC.

VI.41. Answer a.
This patient meets criteria for a diagnosis of autoimmune hepatitis–PBC overlap syndrome. Patients with small duct PSC do not typically have positive AMA or γ-globulin results, and the liver typically has nonspecific histologic changes, including bile ductular fibrosis. Hepatic sarcoidosis is not associated with positive serum autoantibodies, and the liver histologic features are characterized by noncaseating granulomas involving the portal tracts. While many features in this case can be attributed to drug-induced autoimmune hepatitis, the presence of a positive serum AMA and lymphocytic cholangitis rule out this possibility. Given the positive serum AMA, the diagnosis of AMA-negative PBC is incorrect.

VI.42. Answer c.
An increasing serum ALP level in a patient with known chronic ulcerative colitis is common with PSC. Given the lack of efficacy of UDCA, beginning therapy with that drug would not be considered the next step for this patient. Since the patient is asymptomatic from IBD, there is also no compelling need to begin azathioprine therapy. Individuals with PSC and IBD have an increased risk of colorectal neoplasia compared with individuals who have IBD alone, and the current recommendation requires immediate surveillance colonoscopy with 32 biopsies for PSC and IBD regardless of patient age or duration of IBD. Because of the MRCP findings, liver biopsy is not needed to confirm the diagnosis.

VI.43. Answer c.
This patient presents with signs and symptoms compatible with autoimmune pancreatitis and concurrent involvement with the biliary tree. The detection of an elevated serum IgG4 level above normal limits would confirm the diagnosis in the absence of histology. Liver biopsy may identify an excess number of IgG4-producing cells but is not the standard way of confirming the diagnosis. Colonoscopy would be reasonable to perform at some point since a minority of patients will also have IBD. Measurement of serum AMA is not necessary since PBC is not a diagnostic consideration.

VI.44. Answer a.
Amoxicillin-clavulanate was the single most common agent responsible for DILI in the DILIN study (US registry), the Spanish registry, and the Iceland population-based study. Acetaminophen and methotrexate do not produce idiosyncratic DILI; rather, they result in an intrinsic or predictable drug injury. Phenytoin is a common cause of DILI but not the most common.

VI.45. Answer c.
In a randomized double-blind, controlled trial, patients with nonacetaminophen-related acute liver failure were given *N*-acetylcysteine (by 72-hour infusion) or placebo. The benefits of *N*-acetylcysteine were seen primarily in patients with early-stage acute liver failure and coma grade I or II (52% vs 30% transplant-free survival), but not in those with advanced coma grade (III or IV) at randomization. The patient in this question has acute liver failure (no previous liver disease, with new-onset coagulopathy and hepatic encephalopathy) and does not have asterixis (consistent with grade I hepatic encephalopathy); therefore, she would benefit from *N*-acetylcysteine.

VI.46. Answer c.
Hepatitis E IgM should be checked in this patient who has suspected DILI. The previous, self-limited illness could be consistent with symptoms of hepatitis. Eating raw pork or deer meat is a risk factor for hepatitis E. The possibility of HEV involvement in suspected DILI cases was recently evaluated. Hepatitis E IgG serologies were positive in 16% (50 of 318) of patients in the DILIN series; 3% had positive HEV IgM, suggestive of acute HEV infection. In an NHANES study of 18,695 participants in the United States, 21% were HEV seropositive, suggesting that HEV should no longer be considered a disease found only in developing countries. One should consider checking HEV serology for patients with suspected DILI and a hepatocellular injury pattern.

VI.47. Answer a.
Individuals with chronic alcohol use and ingestion of multiple supratherapeutic doses of acetaminophen are at increased risk of acetaminophen hepatotoxicity due to induction of the CYP2E1 enzyme and increased production of the hepatotoxic metabolite *N*-acetyl-*p*-benzoquinone imine.

VI.48. Answer c.
Chronic alcohol use with multiple supratherapeutic doses of acetaminophen is a risk factor for hepatotoxicity because CYP2E1 is induced and more *N*-acetyl-*p*-benzoquinone imine is formed. Acute alcohol ingestion is not a risk factor and may be protective against hepatotoxicity with normal or even mildly supratherapeutic doses of acetaminophen. Chronic alcohol use with normal acetaminophen doses is not a risk factor for hepatoxicity.

VI.49. Answer e.
Carnitine is the treatment of choice for valproate hepatotoxicity with features of hepatic encephalopathy. Carnitine deficiency may be one explanation for the hepatotoxicity and hyperammonemia related to valproate toxicity. Carnitine may attenuate the effect of valproate hepatotoxicity.

VI.50. Answer e.
This clinical scenario (fatigue and pruritus in a middle-aged woman) is highly suspicious for PBC. AMA is the most diagnostic laboratory test available. Xanthelasmas are common with elevated lipids (often mostly high-density lipoprotein cholesterol) and can be a telltale feature of PBC.

VI.51. Answer c.
The biopsy findings show periductal onion skin fibrosis with edema and mild inflammatory infiltrate, which is diagnostic for PSC. This patient is at higher risk since PSC is associated with ulcerative colitis (regardless of whether it is in remission).

VI.52. Answer e.
This patient has PBC. The only medication shown to delay progression of PBC and delay time to liver transplant is ursodiol at a dose of 13 to 15 mg/kg daily. All other listed choices have been investigated and have not been found to be advantageous.

VI.53. Answer c.
This patient has autoimmune hepatitis with typically elevated levels of aminotransferases, SMA, ANA, and IgG. Synthetic function is preserved, although the bilirubin elevation reflects hepatocellular injury. The ferritin is an inflammatory response marker and not a reflection of iron overload in this 28-year-old woman. A liver biopsy is generally recommended (but not absolutely required) to make the diagnosis, and it is necessary if there is diagnostic uncertainty or a need for staging the disease (ie, suspicion of advanced fibrosis or cirrhosis).

VI.54. Answer d.
With conventional therapy of steroids with or without azathioprine, expected response rates are 90% biochemical improvement within 2 weeks (histologic improvement lags by 3-8 months). Histologic remission occurs in 55% to 65% of patients by 18 months and in 80% to 85% by 3 years. For the 10% who do not have remission, overlap syndrome or Wilson disease should be considered.

VI.55. Answer e.
NASH and ASH are indistinguishable histologically. History and clinical examination differentiate the 2 diagnoses.

VI.56. Answer a.
Fatty liver disease from alcohol is reversible. With continued high-volume intake of alcohol, approximately 20% to 30% of patients will progress to advanced liver disease after years of overindulgence.

VI.57. Answer c.
The albumin level becomes deranged with cirrhosis or malnutrition and may not be abnormal in acute alcoholic hepatitis. The other features are significantly associated with poor outcome with acute alcoholic hepatitis (the laboratory tests are used in determining either the Maddrey discrimination function or the MELD score).

VI.58. Answer b.
Acetaminophen toxicity is a "therapeutic misadventure." Although acute viral hepatitis and shock liver are possible diagnoses, the history of back pain suggests that the diagnosis is most likely related to acetaminophen ingestion. Shock liver would be more likely if the patient were hypotensive (and thus unlikely to present to the clinic). If the patient had acute hepatitis A, the ALT:AST ratio would more likely be greater than 1:1, and he would generally present as physically unwell. With a passed gallstone, rarely the enzyme levels may be several thousand units per liter but not usually with liver dysfunction as indicated by the bilirubin and INR results.

VI.59. Answer d.
Weight loss is the first line of therapy for fatty liver. Resuming cholesterol-lowering agents is appropriate if indicated, since studies have shown safety in using statins in chronic liver disease (and they may improve the liver enzyme levels). ANA is frequently positive in fatty liver disease (and ferritin is often elevated). In addition, the normal IgG and SMA results make autoimmune disease very unlikely, particularly with the low level of ANA. Pioglitazone has not been shown to provide a statistically significant benefit in reducing histologic progression of NASH; thus, it is not first-line therapy (but it may be chosen as diabetic therapy in patients with type 2 diabetes mellitus).

VI.60. Answer c.
Pregnant women can have an illness that is not unique to pregnancy. The timing of this patient's illness in the early second trimester is not consistent with Budd-Chiari syndrome, HELLP syndrome, or acute fatty liver of pregnancy. Her symptoms are more consistent with acute hepatitis as opposed to intrahepatic cholestasis. Having a child in day care is a risk factor for hepatitis A.

VI.61. Answer b.
The clinical presentation of ascites, hepatomegaly, and venous collaterals in the postpartum period is most in keeping with Budd-Chiari syndrome. Of the liver diseases associated with pregnancy, Budd-Chiari is most likely to occur in the postpartum period. Furthermore, this patient has a prior history of venous thromboembolism and likely has an undiagnosed hypercoagulable disorder.

VI.62. Answer e.
This patient has ICP, which usually develops in the second or third trimester and is manifested by severe pruritus. Jaundice may be present but is not required for the diagnosis. While patients with biliary obstruction from choledocholithiasis may present with pruritus, pain is usually a feature and this patient does not have any biliary dilatation on ultrasonography. Cholecystectomy is not indicated for asymptomatic gallstones. ICP usually subsides after pregnancy, but medical therapy with UDCA is successful in relieving the pruritus in most cases.

VI.63. Answer e.
Pregnancy is possible after liver transplant but is safest in patients whose transplant was at least 2 years earlier, who adhere to their therapy, and who have normal allograft function. Even in ideal circumstances, pregnancy following transplant should be considered high risk. While some diseases may recur or flare during pregnancy (eg, viral hepatitis, autoimmune hepatitis), this patient's disease would not recur unless she were reexposed to the agent that caused her DILI. Mycophenolate mofetil is associated with birth defects and is contraindicated. Pregnancy is associated with an increased risk of acute cellular rejection but not with chronic (ductopenic) rejection.

VI.64. Answer a.
This patient is critically ill with acute liver failure occurring during the third trimester of pregnancy. The clinical scenario is most consistent with acute fatty liver of pregnancy. While

the HELLP syndrome may also develop in the third trimester, patients with HELLP syndrome have anemia and a low platelet count and are typically not jaundiced. Acute Budd-Chiari syndrome most commonly occurs in the postpartum period. Hepatotoxicity from over-the-counter cold remedies (which frequently contain acetaminophen) is a consideration, but it would be uncommon in the absence of overdose, and patients with acetaminophen hepatotoxicity typically present with aminotransferase levels of several thousand units per liter. The incubation period for acute hepatitis A would be longer than the 1 week since the patient's travel.

VI.65. Answer c.
This patient has multicentric HCC occurring with cirrhosis and portal hypertension. The CT imaging features meet the noninvasive diagnostic criteria (arterial hyperenhancement with portal venous washout), so a biopsy is not necessary. Hepatectomy would be contraindicated in the presence of clinically evident portal hypertension. Unfortunately, the tumor burden is beyond the accepted criteria for transplant (Milan criteria: single lesion ≤5 cm in diameter, or up to 3 lesions that are each ≤3 cm in diameter, with no macrovascular invasion or extrahepatic spread). This patient should be treated with locoregional therapy such as transarterial chemoembolization.

VI.66. Answer b.
This patient is highly symptomatic from his liver disease and would benefit from transplant. Given his low MELD score, he is not likely to be allocated a deceased donor organ in a timely fashion, so he would be best served by living donor transplant if a suitable living donor were available. There is no evidence of cholangiocarcinoma at the present time, and among selected patients with cholangiocarcinoma, good outcomes can be obtained with transplant. Although his prior abdominal surgery does make the transplant operation more difficult (because of adhesions), this alone is not a contraindication to transplant. While research has shown that transplant improves 1-year survival among patients with a MELD score of 15 or higher, this patient is sufficiently symptomatic to consider transplant at this time if a suitable living donor is available.

VI.67. Answer a.
Anastomotic biliary strictures are a common complication following transplant and often occur in this time frame. While ischemic biliary stricture is important in the differential diagnosis, the patency of the hepatic artery would argue against this. It would be very uncommon for PSC to recur this early after transplant. While cholangitis can complicate biliary strictures, the absence of fever or pain argues against this diagnosis. Acute cellular rejection is also important in the differential diagnosis, but it would typically manifest with larger elevations in the aminotransferase levels.

VI.68. Answer b.
This patient presents with typical features of CMV infection with end-organ (gut) involvement. CMV infection most commonly occurs 3 to 12 months following transplant. Patients who require higher doses of immunosuppression or who require antibody therapy (as this patient did) are at increased risk for CMV disease. Patients with posttransplant CMV infection are often quite ill, often have leukopenia, and may have prerenal azotemia when CMV involves the gastrointestinal tract and causes fluid losses from vomiting or diarrhea. Bile leaks typically occur earlier in the posttransplant period (ie, in the first week after transplant) and typically are associated with significant abdominal pain. Acute cellular rejection may be associated with low-grade fever, but patients are not typically so ill. Anastomotic biliary stricturing would not cause fever (unless associated with ascending cholangitis) and would typically feature jaundice. *Clostridium difficile* infection is an important diagnostic consideration, but the presence of leukopenia, the elevations of the liver enzymes, and the upper gut symptoms (nausea and vomiting) favor the diagnosis of CMV infection.

VI.69. Answer c.
Various conditions beyond decompensated cirrhosis may be best treated with transplant. Posttransplant outcomes have been good for selected patients with primary liver malignancies, such as HCC and cholangiocarcinoma. Patients with pulmonary vascular complications of liver disease, including portopulmonary hypertension and hepatopulmonary syndrome, also benefit from transplant. Certain metabolic diseases that manifest with extrahepatic symptoms but are caused by defective hepatic metabolic processes (eg, primary hyperoxaluria, familial amyloid polyneuropathy) may be cured with liver transplant. When not part of a clinical trial, transplant is generally considered contraindicated if patients have metastatic malignancy.

VII

Pancreas and Biliary Tree

36

Acute Pancreatitis[a]

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Acute pancreatitis is an inflammatory condition characterized by severe abdominal pain and locoregional and systemic inflammatory complications. More than 200,000 new cases of acute pancreatitis occur in the United States each year, and its incidence is on the rise. Twenty percent of acute pancreatitis is severe, and about 5% of all patients with pancreatitis die as a result of the disease. Hence, key management principles include prompt diagnosis, triage of severe pancreatitis to aggressive care, and characterization of the cause to prevent recurrence. Necrotizing pancreatitis accounts for most of the morbidity and nearly all the mortality associated with acute pancreatitis.

Pathophysiology

The pathophysiology of acute pancreatitis begins with inappropriate activation of trypsin within the acinar cell. Activated intracellular trypsin, in turn, activates a cascade of digestive enzymes that leads to autodigestion and cellular injury. Acinar cell injury leads to inflammation by recruitment of inflammatory cells through cytokines and other mediators. In 80% of cases, acute pancreatitis is mild and self-limited, with little or no long-term sequelae to the pancreatic parenchyma or systemic toxicity. In 20% of cases, severe acute pancreatitis develops, leading in the early phase to the systemic inflammatory response syndrome (SIRS), organ failure (hypotension, renal failure, and acute respiratory distress syndrome), and pancreatic necrosis. Most of the morbidity and mortality early in the course of severe acute pancreatitis is due to systemic toxicity secondary to SIRS, whereas late mortality, beyond 10 to 14 days, is related to pancreatic necrosis and infection.

Clinical Presentation and Diagnosis

The clinical presentation of patients with acute pancreatitis ranges from mild, nonspecific epigastric pain to catastrophic acute medical illness. The pain of acute pancreatitis generally is located in the epigastrium and radiates into the back in approximately 50% of patients. The onset of pain is usually swift, reaching maximum intensity within an hour. Pain is often unbearable and generally persists without episodic improvement for at least 24 hours, in the absence of intervention. Pain often is accompanied by nausea and vomiting. In severe episodes of acute pancreatitis, SIRS dominates and patients appear systemically ill, with fever, tachycardia, tachypnea, and hypotension.

The differential diagnosis of acute pancreatitis is broad and includes most of the important causes of abdominal pain, including mesenteric ischemia and infarction, perforated peptic ulcer, symptomatic cholelithiasis, dissecting aortic aneurysm, intestinal obstruction, and inferior wall myocardial infarction.

By consensus, the diagnosis of acute pancreatitis requires 2 of the following 3 findings:

1. Abdominal pain that is consistent with acute pancreatitis
2. Serum level of amylase or lipase >3 times the upper limit of the reference range (ULRR)
3. Findings of acute pancreatitis seen on cross-sectional imaging by computed tomography (CT), ultrasonography, or magnetic resonance imaging (MRI)

[a] Portions previously published in Baron TH, Morgan DE. Acute necrotizing pancreatitis. N Engl J Med. 1999 May 6;340(18):1412-7. Used with permission.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; HAPS, harmless acute pancreatitis score; ICU, intensive care unit; MRI, magnetic resonance imaging; SIRS, systemic inflammatory response syndrome; ULRR, upper limit of the reference range

These criteria indicate that the diagnosis of acute pancreatitis can be made on the basis of pain and diagnostic levels of amylase and lipase, obviating the need for imaging in many cases. If the serum levels of amylase or lipase are only modestly elevated (<3 times the ULRR), the lack of specificity of this finding dictates the need for imaging, most commonly CT, to establish the diagnosis. The definition also provides means to diagnose acute pancreatitis when a patient cannot give a clinical history because of altered mental status or the severity of the acute presentation. When performed more than 48 hours after presentation, CT with contrast enhancement also provides important prognostic information, as discussed below.

Both amylase and lipase levels are usually increased during the acute phase of pancreatitis. Amylase elevations are more than 90% sensitive for acute pancreatitis, and 3-fold elevations are more than 90% specific, yet with lower sensitivity. The serum lipase level generally is preferred to the serum amylase level because lipase is more specific to the pancreas, and lipase elevations, therefore, tend to reflect pancreatic pathology for a longer interval compared with amylase levels, which become lost in the noise of normal basal amylase from multiple sources. Amylase and lipase can be elevated from bowel ischemia, obstruction, or perforation leading to enteric leakage and systemic absorption of intraluminal pancreatic enzymes. The amylase level is also increased nonspecifically in various nongastrointestinal conditions (Box 36.1), including macroamylasemia, diseases of the parotid glands, and some carcinomas.

Macroamylasemia is a benign condition that may cause confusion when present with other causes of abdominal pain. Macroamylase is a macromolecular aggregation of amylase molecules that are poorly excreted by the kidney, yielding chronically fluctuating elevations in serum amylase, which are generally less than twice the ULRR. Infrequent disease associations have been reported. The diagnosis of macroamylasemia may be suggested by a low ratio of amylase to creatinine clearance and is easily established by immunologic assay.

Box 36.1. Differential Diagnosis of Elevated Pancreatic Enzymes

Amylase: cleared by reticuloendothelial system excretion *and* renal filtration

- Pancreatic inflammation (acute and chronic pancreatitis) or trauma; ERCP
- Salivary inflammation, obstruction, or trauma
- GI inflammation, obstruction, perforation, or ischemia
- Ovarian disease or cysts; ectopic pregnancy
- Cancer of the ovary, prostate, lung, breast, or thymus; multiple myeloma; pheochromocytoma
- Macroamylasemia: rarely associated with celiac disease, ulcerative colitis, rheumatoid arthritis, lymphoma, HIV, or monoclonal gammopathy
- Other causes, including renal failure, burns, acidosis, anorexia nervosa, bulimia, cerebral trauma, and drugs

Lipase: renal filtration and tubular resorption (increased half-life)

- Pancreatic inflammation (acute and chronic pancreatitis), trauma, or tumors
- GI: acute cholecystitis, bowel obstruction or infarction, duodenal ulcer, or celiac disease

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography GI, gastrointestinal tract; HIV, human immunodeficiency virus.

Importantly, the absolute level of either lipase or amylase does not have prognostic value and is not predictive of severity. After the diagnosis of acute pancreatitis has been made, serial measurements of lipase and amylase levels have no prognostic value in guiding management and should be avoided. Resolution of elevated enzyme levels may lag behind clinical improvement, so they should not be monitored to guide reinstitution of oral intake. Reassessment of enzyme levels may be useful in selected settings when clinical relapse is suspected.

Plain abdominal radiographs are frequently normal at presentation with acute pancreatitis, but they are useful in excluding perforation. A nonspecific ileus may be present as well as a focally dilated small-bowel loop, the so-called sentinel loop. *Colon-cutoff sign* refers to the abrupt narrowing of the gas in the transverse colon seen on a plain film of the abdomen in the vicinity of the body of the pancreas.

Abdominal ultrasonography is frequently nondiagnostic in acute pancreatitis because overlying bowel gas may obscure the pancreas. However, ultrasonography is sensitive for detecting gallstones and, thus, adds clinical information about the underlying cause of the pancreatitis and should be used for patients with an intact gallbladder.

Etiology

Once acute pancreatitis is diagnosed, characterization of the underlying cause is important for prevention of future episodes. The causes are diverse and can be variably grouped by their mechanisms (Box 36.2). Gallstones are the most common cause of acute pancreatitis in middle and upper socioeconomic groups in the United States, while alcohol is the predominant cause in lower socioeconomic populations. Gallstones cause acute

Box 36.2. Etiology of Acute Pancreatitis

- Mechanical: gallstones, biliary sludge, ascariasis, periampullary diverticulum, pancreatic or periampullary cancer, ampullary or papillary stenosis, duodenal stricture or obstruction
- Toxic: ethanol, methanol, scorpion venom, organophoshate poisoning
- Metabolic: hypertriglyceridemia, hypercalcemia
- Drugs: numerous (see Box 36.3)
- Infection

  Viruses: mumps, coxsackievirus, hepatitis B virus, cytomegalovirus, varicella-zoster virus, herpes simplex virus, human immunodeficiency virus
  Bacteria: *Mycoplasma, Legionella, Leptospira, Salmonella*
  Fungi: *Aspergillus*
  Parasites: *Toxoplasma, Cryptosporidium, Ascaris*

- Trauma: post-ERCP, blunt or penetrating abdominal injury, iatrogenic injury, surgery
- Congenital or anatomical: choledochocele, pancreas divisum
- Vascular: ischemia, atheroembolism, vasculitis (polyarteritis nodosa, systemic lupus erythematosus)
- Genetic: *CFTR* and other genetic mutations
- Miscellaneous: pregnancy, renal transplant, alpha$_1$-antitrypsin deficiency, sphincter of Oddi dysfunction (possibly)
- Idiopathic

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography.

pancreatitis by mechanical obstruction of the common channel shared by the bile duct and pancreatic duct, with increased intraductal pressure in the pancreas and possibly pancreatic reflux of bile acids in some cases. Alcohol induces a direct toxic injury to the pancreas.

An important metabolic cause is hypertriglyceridemia; a threshold triglyceride level of 1,000 mg/dL has been established as being causative. Other causes include hypercalcemia, trauma, postoperative state, infections by various agents, endoscopic retrograde cholangiopancreatography (ERCP), and medications.

Drugs are often stated to cause 0.1% to 2% of cases of acute pancreatitis (Box 36.3). Recent studies suggest that rates may be as high as 5% to 10%. Less than half of drug-induced pancreatitis cases are recognized by clinicians, since there are no unique clinical features and most cases are mild. Historically, case reports and small series have enabled drugs to be classified as definite, probable, or possible causes of acute pancreatitis. A greater emphasis on positive reactions to rechallenge, exclusion of other causes, and the temporal relationships between drug use and onset has allowed classification of drugs into 5 risk classes (Badalov classes Ia, Ib, II, III, and IV). Patients at heightened risk for drug-induced pancreatitis include pediatric and elderly patients, female patients, and those with inflammatory bowel disease or human immunodeficiency virus.

Unfortunately, about 15% to 20% of cases of acute pancreatitis are classified as idiopathic because no cause is found even after extensive testing. Several clues to the cause should be kept in mind (Box 36.4). Most useful is early characterization of the serum transaminase levels, since they are often increased transiently in biliary pancreatitis, reflecting liver injury associated with the obstruction of the bile duct. In pancreatitis, an increase in the level of alanine aminotransferase that is greater than 3-fold has a positive predictive value greater than 90% for a biliary source and a sensitivity of about 50%.

Box 36.3. Drugs Reliably Associated With Acute Pancreatitis

- Antimicrobials: erythromycin, clarithromycin, isoniazid, metronidazole, nitrofurantoin, ceftriaxone, trimethoprim-sulfamethoxazole, pentamidine, ampicillin, rifampin, tetracycline
- HIV therapy: didanosine, nelfinavir
- Diuretics: furosemide, chlorothiazide, hydrochlorothiazide
- GI agents: omeprazole, cimetidine, ranitidine, mesalamine, 6-mercaptopurine, azathioprine, hydrocortisone, cyclosporine, lamivudine, interferon, ribavirin, octreotide, propofol
- Cardiac agents: procainamide, α-methyldopa, captopril, enalapril, lisinopril, amiodarone, losartan
- Immunosuppressives or chemotherapeutics: L-asparaginase, cytosine arabinoside, dexamethasone, ifosfamide, paclitaxel, tacrolimus
- Neuropsychiatric agents: valproic acid, clozapine, carbamazepine, risperidone, sertraline
- Other common drugs: bezafibrate, carbimazole, codeine, pravastatin, simvastatin, all-*trans* retinoic acid, acetaminophen, estrogens, alendronate, indomethacin, metformin, naproxen, diclofenac, sulindac, orlistat, danazol, ergotamine

Abbreviations: GI, gastrointestinal tract; HIV, human immunodeficiency virus.

Box 36.4. Etiologic Clues in Acute Pancreatitis (AP)

- Early transaminase elevations (>3 times ULRR) are the best laboratory indicators of biliary AP.
- Normal gallbladder ultrasonographic findings do not exclude biliary AP.
- Finding gallbladder sludge at presentation is equivalent to finding gallstones; subsequent development of sludge is common in fasting and ill patients.
- In hypertriglyceridemic AP (usually triglycerides >1,000 mg/dL), amylase levels may be artificially normal.
- Triglyceride values decrease rapidly when a patient is taking nothing by mouth. Levels should be checked early after diagnosis, and, if normal, they should be rechecked again after resolution of AP.
- Serum calcium may normalize in severe AP, and it should be rechecked after resolution if a cause is not identified.
- Remember cancer in patients older than 50 years; cancer causes 2% of AP, and up to 5% of patients with pancreatic cancer present with AP.
- If a patient is young and AP is idiopathic or recurrent, consider genetic causes.

Abbreviation: ULRR, upper limit of the reference range.

Severity Stratification

Following the diagnosis of acute pancreatitis, it is important to promptly identify patients destined to have severe disease, thus enabling early triage to aggressive monitoring and supportive care. Most patients (80%) have interstitial or edematous pancreatitis with a mild self-limited course and very low mortality. Twenty percent have moderate to severe disease with significant local morbidity and a mortality rate of about 20%. The majority of these patients have necrotizing pancreatitis. Several severity-of-illness scoring systems have been devised to identify patients at risk for complications; some systems are remarkably simple, while others are more complex or require serial investigations over 48 hours.

Patient Characteristics

Risk factors for a severe course are age older than 55 years, obesity (body mass index >30, calculated as weight in kilograms divided by height in meters squared), organ failure at admission (especially renal or respiratory), and pleural effusions. Patients with these findings require close observation and perhaps even admission to an intensive care unit.

The *Ranson criteria* consist of 11 clinical signs with prognostic significance: 5 criteria are measured at the time of admission, and 6 are measured between admission and 48 hours later (Table 36.1). The number of Ranson criteria correlates with the incidence of systemic complications and the presence of pancreatic necrosis. The main disadvantage of the Ranson criteria is that they may not be evaluated until 48 hours after admission.

The *Acute Physiology and Chronic Health Evaluation* (APACHE) *II* scoring system is based on 12 physiologic variables, patient age, and previous history of severe organ system insufficiency or immunocompromised state (Table 36.2). It allows stratification of the severity of illness on admission and may be recalculated daily. Although the APACHE II scoring system has the advantage of being completed at the initial presentation as well as being repeated daily, it is cumbersome to use.

Table 36.1. Ranson Criteria for Assessing the Severity of Acute Pancreatitis

Measured at Admission	*Measured During Initial 48 h*
Age >55 y	Hematocrit decreases >10%
Leukocytes >16,000/μL	Serum urea nitrogen increases >5 mg/dL
Blood glucose >200 mg/dL	Serum calcium <8 mg/dL
Serum lactate dehydrogenase >350 U/L	Arterial Pao_2 <60 mm Hg
Serum aspartate aminotransferase >250 U/L	Base deficit >4 mEq/L
	Fluid sequestration >6 L

Adapted from Banks PA. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 1997 Mar;92(3):377-86. Used with permission.

The *Atlanta classification* is the most widely used clinical system for indicating the severity of acute pancreatitis. This classification recognizes mild (interstitial) and severe (necrotizing) types of the disease. It classifies an attack of acute pancreatitis as severe if any of the following criteria are met:

1. Organ failure with ≥1 of the following: shock (systolic blood pressure <90 mm Hg), pulmonary insufficiency (Pao_2 <60 mm Hg), renal failure (serum creatinine level >2 mg/dL after rehydration), or gastrointestinal tract bleeding (>500 mL in 24 hours)
2. Local complications such as pseudocyst, abscess, or pancreatic necrosis
3. Three or more Ranson criteria
4. Eight or more APACHE II criteria

Terms such as *phlegmon, hemorrhagic pancreatitis, infected pseudocyst*, and *persistent pancreatitis* are not used because they can cause confusion.

Since the scoring systems outlined above are cumbersome and often require 48 hours of observation, clinical investigators have sought a single biochemical marker for severity. The acute phase reactant C-reactive protein has been shown to predict severity, but its level generally has to increase to more than 150 mg/L over 36 to 72 hours after admission before it becomes useful. Other simple markers have included serum glucose and creatinine, but all have poor specificity.

Hemoconcentration due to extravasation of fluid into third spaces, reflected by an increase in the serum hematocrit, has been proposed as a simple reliable predictor of necrotizing pancreatitis. This is particularly true if the hematocrit does not decrease after 24 hours, which likely reflects inadequate volume resuscitation. According to other reports, hemoconcentration, although quite sensitive, is nonspecific in that it "overpredicts" severity. This is the problem with most of the single biochemical markers determined on admission.

The *harmless acute pancreatitis score* (HAPS) is designed to identify patients who will have a mild, self-limited course rather than severe disease. Its 3 components, which can be measured within 30 minutes, include 1) absence of rebound tenderness on physical examination, 2) a normal hematocrit, and 3) a normal serum creatinine level. The presence of all 3 components was found to predict a mild course with 96% specificity and a 98% positive predictive value. This has been validated in several European studies and may guide clinicians in at least identifying patients who do not need aggressive early management.

Abdominal Imaging Studies

Disruption of pancreatic perfusion causes pancreatic necrosis and is detectable when an intravenous contrast agent is given during CT imaging (Figures 36.1 and 36.2). The *Balthazar score* is a CT classification system for estimating the severity of acute pancreatitis according to the proportion of pancreas that is not perfused (reflecting necrosis) and the number of fluid collections. High mortality can be expected if the Balthazar CT severity index

Table 36.2. Acute Physiology and Chronic Health Evaluation (APACHE) II Scoring System[a,b]

	Physiology Points								
Variable	*4*	*3*	*2*	*1*	*0*	*1*	*2*	*3*	*4*
Rectal temperature, °C	≥41.0	39.0-40.9	. . .	38.5-38.9	36.0-38.4	34.0-35.9	32.0-33.9	30.0-31.9	≤29.9
Mean blood pressure, mm Hg	≥160	130-159	110-129	. . .	70-109	. . .	50-69	. . .	≤49
Heart rate, beats per minute	≥180	140-179	110-139	. . .	70-109	. . .	55-69	40-54	≤39
Respiratory rate, breaths per minute	≥50	35-49	. . .	25-34	12-24	10-11	6-9	. . .	≤5
Oxygenation, kPa[c]									
FIO_2 ≥50% $AaDO_2$	66.5	46.6-66.4	26.6-46.4	. . .	<26.6	. . .	. . .	. . .	. . .
FIO_2 >50% Pao_2	. . .	. . .	. . .	. . .	>9.3	8.1-9.3	. . .	7.3-8.0	<7.3
Arterial pH	≥7.70	7.60-7.69	. . .	7.50-7.59	7.33-7.49	. . .	7.25-7.32	7.15-7.24	<7.15
Serum sodium, mEq/L	≥180	160-179	155-159	150-154	130-149	. . .	120-129	111-119	≤110
Serum potassium, mEq/L	≥7.0	. . .	6.0-6.9	. . .	5.5-5.9	3.5-5.4	3.0-3.4	2.5-2.9	<2.5
Serum creatinine, mg/dL	≥3.5	2.0-3.4	1.5-1.9	. . .	0.6-1.4	. . .	<0.6	. . .	. . .
Packed cell volume, %	≥60	. . .	50-59.9	46-49.9	30-45.9	. . .	20-29.9	. . .	<20
White blood cell count, /μL	≥40,000	. . .	20,000-39,900	15,000-19,900	3,000-14,900	. . .	1,000-2,900	. . .	<1,000

Abbreviations: $AaDO_2$, alveolar-arterial oxygen difference; FIO_2, fraction of inspired oxygen.

[a] APACHE II score = acute physiology score + age points + chronic health points.

[b] Other points are determined as follows:

- Glasgow Coma Scale: score is subtracted from 15 to obtain points.
- Age: <45 years = 0 points; 45-54 years = 2 points; 55-64 years = 3 points; 65-75 years = 5 points; >75 years = 6 points.
- Chronic health points (must be present before hospital admission): 5 points are added for an emergency surgical or nonsurgical patient, and 2 points are added for an elective surgical patient who has chronic liver disease with hypertension or previous liver failure, encephalopathy, or coma; chronic heart failure (New York Heart Association class IV); chronic respiratory disease with severe exercise limitation, secondary polycythemia, or pulmonary hypertension; dialysis-dependent kidney disease; or immunosuppression (eg, radiotherapy, chemotherapy, recent or long-term high-dose corticosteroid therapy, leukemia, AIDS).

[c] If FIO_2 ≥50%, the alveolar-arterial gradient is assigned points. If FIO_2 <50%, partial pressure of oxygen is assigned points.

Adapted from Banks PA. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 1997 Mar;92(3):377-86. Used with permission.

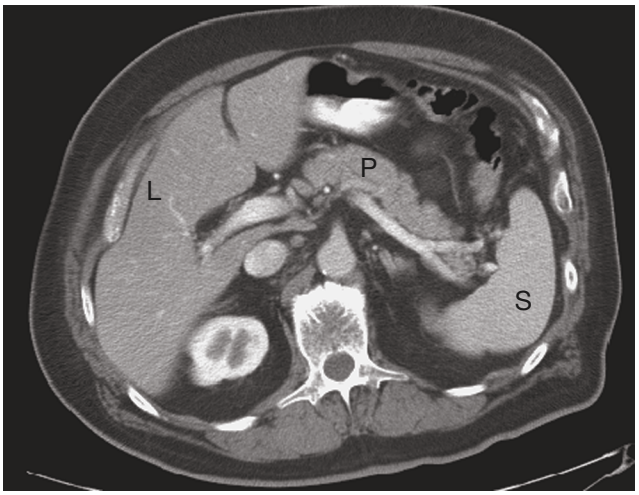

Figure 36.1. Normal-Enhanced Computed Tomography of the Pancreas. Note that the pancreas (P) has a uniform enhancement intermediate between that of the liver (L) and spleen (S).

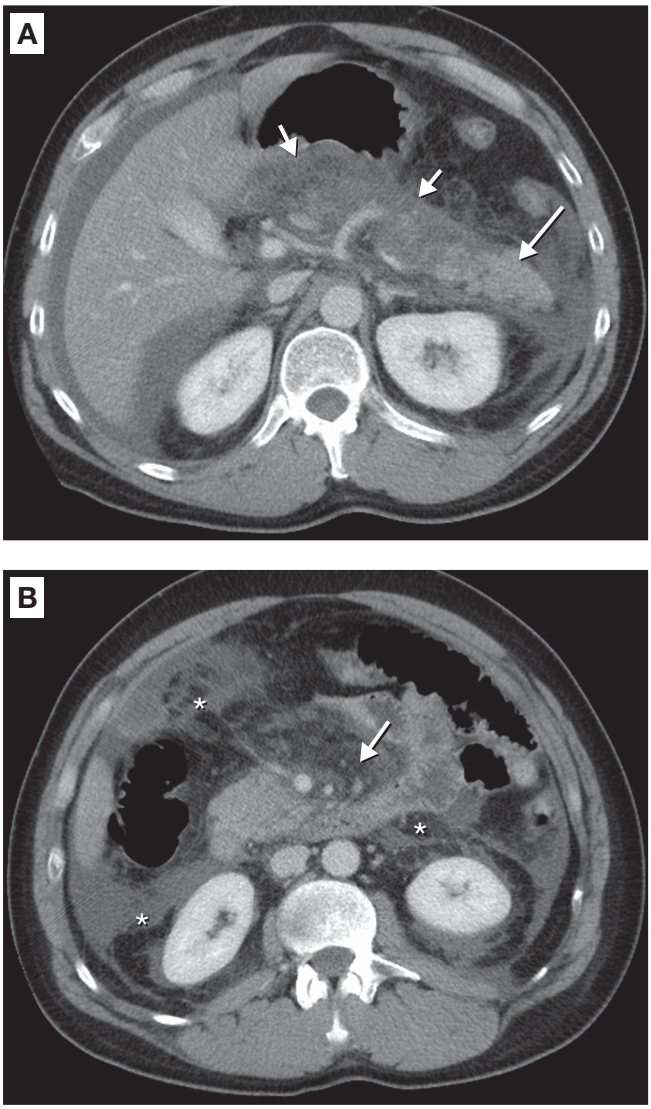

Figure 36.2. Acute Necrotizing Pancreatitis. A, The patient had severe biliary pancreatitis. Note that the density of the necrotic portion of the pancreas (short arrows) is less than that of the normal-enhancing pancreas in the tail (long arrow). B, Note the necrosis in the body (arrow) and the peripancreatic edema (asterisks). The pancreatic head is well perfused.

is 7 or more. Patients with acute pancreatitis who have normal CT findings have a good prognosis. There is good correlation between the failure of more than 30% of the pancreas to enhance on contrast-enhanced CT and the finding of pancreatic necrosis at surgery or autopsy. As the degree of necrosis increases, there is a corresponding increase in morbidity and mortality.

Features of poor perfusion are often lacking in the first 48 to 72 hours after the onset of acute pancreatitis. Hence, CT scans performed early in the course of disease may be falsely reassuring when necrosis is not identified. In definite cases of acute pancreatitis, contrast-enhanced CT can be deferred for 2 to 3 days and then—only if the patient's condition is deteriorating or not responding to supportive care—performed in order to confirm the presence of necrosis and guide appropriate therapy. Recently, MRI has been compared prospectively with CT in the context of severe pancreatitis and found to be reliable for staging severity, to have predictive value for the prognosis of the disease, and to have fewer contraindications than CT. It may also detect disruption of the pancreatic duct, which can occur early in the course of acute pancreatitis.

Treatment

Keys to management of all cases of acute pancreatitis are 1) early estimation of severity (as outlined above), 2) aggressive fluid supplementation, 3) analgesia, and 4) elucidation and treatment of the underlying cause. In the absence of heart failure or chronic oliguria, lactated Ringer solution or normal saline should be administered intravenously at a rate of at least 250 to 300 mL hourly and titrated according to urine output and change in the serum urea nitrogen or creatinine level.

Analgesia for pain control requires narcotic-strength agents, typically fentanyl or morphine, administered as patient controlled analgesia. Although in animal experiments, morphine has caused spasm of the sphincter of Oddi, there is no definite evidence that morphine worsens the disease in humans.

Interstitial acute pancreatitis can be managed with supportive care on a general hospital ward without need for monitoring in an intensive care unit (ICU). Nasogastric tubes do not improve disease outcome, they increase patient discomfort, and they are generally not indicated. However, nasogastric tubes may decrease symptoms in patients with extreme nausea, vomiting, and ileus. Empirical use of antibiotics should be avoided in patients with interstitial pancreatitis because these agents do not alter the outcome. Nutritional support (discussed below) is indicated only if the patient is expected to receive nothing by mouth for 1 or more weeks. For mild interstitial pancreatitis, recent studies have shown that early oral feeding, as tolerated, is safe.

Specific therapy for identified causes of acute pancreatitis should be instituted early to prevent recurrence of acute episodes. This includes discontinuation of suspected medications that might have induced pancreatitis, institution of therapy for hypertriglyceridemia, and performance of cholecystectomy for suspected biliary pancreatitis. Cholecystectomy should be performed before hospital dismissal to prevent early recurrence of acute pancreatitis among patients who delay their return or do not return for follow-up. If the patient is a poor surgical candidate because of severe coexisting medical illness, ERCP with biliary

sphincterotomy may be a good alternative to cholecystectomy, especially if ultrasonography shows only sludge or small stones.

If biliary stone disease, hyperlipidemia, and medications are excluded as causes, abdominal CT should be performed to exclude anatomical causes of pancreatic ductal obstruction, such as a pancreatic or ampullary mass lesion or intraductal papillary mucinous neoplasm, especially in patients older than 50 years. For elderly patients with negative CT findings, consideration should be given to performing endoscopic ultrasonography, magnetic resonance cholangiopancreatography, or ERCP after the acute changes have resolved.

Severe acute pancreatitis, with or without pancreatic necrosis, requires aggressive medical management, with greater emphasis on fluid supplementation and the prevention and early diagnosis of infection. In recent years, the management of these patients has shifted from early surgical débridement (necrosectomy) to intensive medical care.

Aggressive intravenous fluid replacement counteracts intravascular volume depletion caused by third space losses, vomiting, fever, and the vascular permeability related to SIRS. Intravascular volume depletion causes hemoconcentration, low urine output, azotemia, tachycardia, and hypotension, thus compromising the blood supply of the pancreas, which contributes to the development of pancreatic necrosis with its attendant complications. Evidence from experimental models supports the concept that early aggressive fluid resuscitation minimizes or aborts pancreatic necrosis and improves survival. Similarly, considerable evidence from large clinical databases supports the importance of aggressive fluid resuscitation. A single randomized trial with 40 patients suggested that hydration using lactated Ringer solution yielded a lower rate of infectious complications compared with hydration with normal saline. In 1 study, pancreatic necrosis developed in all patients who had evidence of hemoconcentration at admission and whose hematocrit increased during the first 24 hours (indicating inadequate volume resuscitation). It is critically important that the adequacy of fluid resuscitation be monitored carefully following the decrease in hematocrit at 12 and 24 hours, with frequent serial checking of vital signs and measurement of urinary output. Serum levels of electrolytes, calcium, magnesium, and glucose and oxygenation should all be monitored and supported or corrected, as indicated. These issues may require admission to an ICU.

Early mortality during the first week or 2 is primarily due to multisystem organ failure resulting from SIRS. Systemic complications include adult respiratory distress syndrome, acute renal failure, shock, coagulopathy, hyperglycemia, and hypocalcemia. These complications are managed with endotracheal intubation, aggressive fluid resuscitation, fresh frozen plasma, insulin, and calcium, as needed.

Nutritional Support

Nutritional support is often indicated to meet increased metabolic demands and to rest the pancreas during the prolonged fasting state of acute pancreatitis. Multiple randomized prospective studies of severe acute pancreatitis have compared total parenteral nutrition with enteral feeding through a nasoenteric feeding tube placed under endoscopic or radiographic guidance. Enteral feeding yields significantly fewer total and infectious complications, a 3-fold decrease in the cost of nutritional support, and improvement in the acute phase response and disease severity scores, compared with parenteral (intravenous) nutrition. Enteral nutrition helps preserve the mucosal barrier of the gut and reduces translocation of bacteria from the gut, thus decreasing the rate of infected necrosis. A recent meta-analysis of nutritional therapy for patients with acute pancreatitis reported that, compared with parenteral nutrition, enteral nutrition was associated with a significantly lower incidence of infections, a decreased number of surgical interventions to control pancreatitis, and a reduction in mortality. Enteral nutrition should be considered the standard of care for patients with severe acute pancreatitis.

Ideally, enteral nutrition is delivered to the jejunum or at least to the postpyloric gut. Placement of the feeding tube into the jejunum theoretically decreases stimulation of the inflamed pancreas, but radiologic or endoscopic guidance adds expense and is not readily available in all community hospitals. From studies with contradictory results, nasogastric feeding may or may not be as safe and beneficial as nasojejunal feeding. This issue requires further study.

Prophylactic Antibiotics

The prevention of infection is critical because secondary infection of necrosis develops in 30% of patients with acute necrotizing pancreatitis and accounts for more than 80% of deaths due to acute pancreatitis. Most infections occur after 10 days, are monomicrobial, and are due to enteric bacteria (gram-negative rods or enterococci). The use of prophylactic antibiotics, while theoretically attractive, is controversial and their value unproven despite at least 7 prospective trials of various quality. Recent meta-analyses have concluded that prophylactic antibiotics cannot be recommended for preventing pancreatic infection, since there is no difference in the rate of infected necrosis, systemic complications, or mortality between the treated and control groups. Yet another meta-analysis and a systematic review suggested that use of imipenem reduces mortality in severe acute pancreatitis, but not the rate of infected necrosis. There is concern, however, that the use of potent broad-spectrum antibiotics may increase the risk of secondary or superimposed fungal infections. Published guidelines do not recommend prophylactic antibiotics for patients with necrotizing pancreatitis. Certainly, there is no indication for routine antibiotics in treating mild or interstitial pancreatitis.

Clinically, patients with severe pancreatitis often have features of sepsis, including fever, leukocytosis, and organ failure in the first 7 to 10 days. During this interval, while sources of potential infection are being investigated and after appropriate cultures are obtained, antibiotic therapy is appropriate. Imipenem or equivalent coverage (noted below) is used most often. However, if cultures are negative, antibiotic therapy should be discontinued.

Detection of Pancreatic Infection

Sterile or infected acute necrotizing pancreatitis can be difficult to distinguish clinically, because either may produce fever, leukocytosis, and severe abdominal pain. Without intervention, the mortality rate for patients with infected acute necrotizing pancreatitis is nearly 100%. The bacteriologic status of the pancreas can be determined with CT-guided fine-needle aspiration of pancreatic and peripancreatic tissue or fluid. This aspiration method is safe, accurate (96% sensitivity and 99% specificity), and recommended for patients with acute necrotizing pancreatitis whose condition deteriorates clinically or does not improve despite aggressive supportive care. Ultrasonographically guided aspiration may have lower sensitivity and specificity, but it can be performed at the bedside. If initial sampling is negative, surveillance aspiration may be advisable

on a weekly basis if the patient is not improving. If CT-guided sampling documents the presence of gram-negative organisms, appropriate choices for antibiotics include a carbapenem, a fluoroquinolone with metronidazole, or a third-generation cephalosporin with metronidazole. If Gram stains show gram-positive organisms, the addition of vancomycin is appropriate. In all cases, antibiotic coverage can be narrowed or expanded once the identity and sensitivities of the organism are known.

Therapy for Pancreatic Necrosis

Débridement of pancreatic necrosis is indicated for confirmed infection of extensive necrosis and for infected or sterile necrosis with expanding fluid collections causing severe pain or gut obstruction. Ideally, débridement for pain or obstruction should be deferred until the necrosis and fluid collections have consolidated, with development of so-called walled-off pancreatic necrosis (Figure 36.3). This typically occurs over 4 to 6 weeks. Débridement can be accomplished by endoscopic, percutaneous radiologic, or minimally invasive or open surgical approaches. A recent randomized multicenter study compared open surgical necrosectomy to a "step-up" approach, which began with percutaneous drainage and, if necessary, advanced to use of minimally invasive retroperitoneal surgical necrosectomy. The step-up approach group had lower rates of major complications, new-onset multiorgan failure, incisional hernias, and new-onset diabetes mellitus. In this group, 35% of patients received percutaneous drainage only. The death rate did not differ significantly.

Role of ERCP

ERCP with biliary sphincterotomy appears to improve outcomes among patients who have severe gallstone pancreatitis with associated cholangitis or biliary obstruction. Studies that exclude patients with biliary obstruction have shown limited or no benefit from early ERCP in severe acute pancreatitis. Hence, improved outcome after ERCP and sphincterotomy in gallstone pancreatitis appears to be the result of reduced biliary sepsis rather than improvement in pancreatitis. When performed, ERCP should ideally be undertaken in the first 48 to 72 hours, since later cholestasis often reflects pancreatic edema rather than stone obstruction, and associated duodenal edema compromises success rates after this interval.

Prognosis

The overall mortality rate for patients with severe acute pancreatitis has decreased to approximately 15% as a result of improved ICU therapies, antibiotics, and deferral of surgery. Early deaths (1-2 weeks after the onset of pancreatitis; approximately 50% of all deaths) are primarily due to multisystem organ failure, and late deaths result from local or systemic infections. The overall mortality rate for patients with sterile acute necrotizing pancreatitis is approximately 10%. The mortality rate is at least 3 times higher if infected necrosis occurs. Patients with sterile necrosis and high severity-of-illness scores (Ranson score or APACHE II score) accompanied by multisystem organ failure, shock, or renal insufficiency have a significantly higher mortality rate.

The long-term clinical endocrine and exocrine consequences of acute necrotizing pancreatitis appear to depend on several factors: the severity of necrosis, the cause of pancreatitis (alcoholic or nonalcoholic), the continued use of alcohol, and the degree of pancreatic débridement. Sophisticated exocrine function studies have shown persistent subclinical exocrine insufficiency in the majority of patients up to 2 years after severe acute pancreatitis. Treatment with pancreatic enzymes should be restricted to patients with symptoms of steatorrhea and weight loss due to fat malabsorption. Although subtle glucose intolerance is frequent, overt diabetes mellitus is uncommon.

Severe necrosis of the head or body of the pancreas may result in disruption of the pancreatic duct, leading to persistent or recurrent fluid collections and symptoms related to mass effect, bowel obstruction, or infection. Management of this disrupted pancreatic duct syndrome often requires surgical resection of the disconnected but functional upstream portion of the gland (distal pancreatectomy) or surgical cyst enterostomy for prolonged diversion of leaking pancreatic juice. In some cases, duct continuity can be reestablished by endoscopic stent

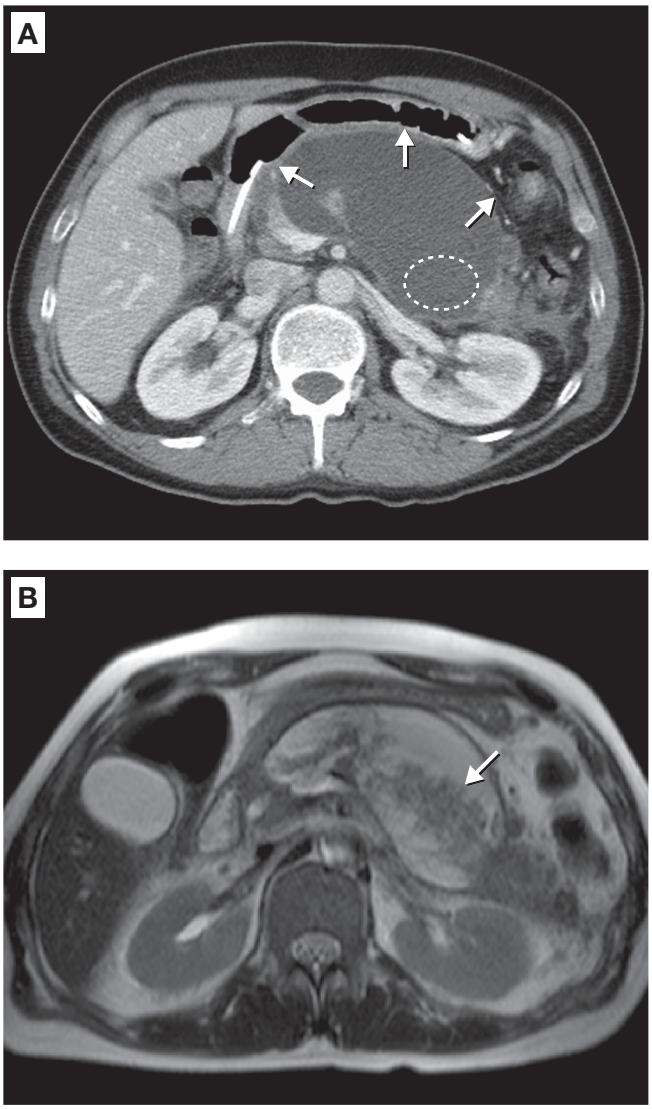

Figure 36.3. Walled-off Pancreatic Necrosis. A, Computed tomographic scan from the same patient as in Figure 36.2 shows that, 6 weeks later, most of the peripancreatic edema has resolved. The necrosis and fluid collection are well contained in the lesser sac, with a discrete wall or rind (arrows). Note that the scan does not image the necrotic debris contained within the fluid collection (broken circle indicates area void of material). B, Magnetic resonance imaging of the same collection shows clear evidence of solid debris (arrow) within the fluid collection, a result of necrosis of the pancreatic body.

placement from the duodenum through the downstream duct and across the disruption. In patients who are poor operative candidates, a chronic fistula can be maintained to the stomach or the duodenum by long-term placement of a transmucosal stent.

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37

Chronic Pancreatitis

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Chronic pancreatitis is an often painful inflammatory condition of the pancreas characterized by progressive fibrosis that leads to irreversible destruction of exocrine and endocrine tissue, resulting eventually in exocrine and endocrine insufficiency. There is considerable heterogeneity in the manifestation and natural history of the condition. Chronic pancreatitis is classified broadly into chronic calcifying pancreatitis, chronic obstructive pancreatitis, and chronic autoimmune pancreatitis.

Chronic calcifying pancreatitis is characterized by recurrent bouts of clinically acute pancreatitis early in the course of the disease, with development of intraductal stones later in the disease course. Steatorrhea and diabetes mellitus develop in the majority of patients. This is the clinical profile of the disease that readily comes to mind when the term *chronic pancreatitis* is used in clinical practice.

Chronic obstructive pancreatitis results from obstruction of the pancreatic duct due to any cause. The disease affects only the portion of the organ that is upstream of the obstruction. It is usually not associated with pancreatic duct stone formation. Although often asymptomatic, partial obstruction can lead to recurrent bouts of clinically acute pancreatitis involving the obstructed part of the gland. Obstructive pancreatitis commonly occurs distally to pancreatic tumors (ductal adenocarcinoma and intraductal papillary mucinous tumor) and postinflammatory strictures following acute or traumatic pancreatitis. Resection of the obstructed distal portion of the pancreas is the preferred treatment of symptomatic disease.

Abbreviations: AIP, autoimmune pancreatitis; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging

Chronic autoimmune pancreatitis, simply known as autoimmune pancreatitis (AIP), is a unique form of chronic pancreatitis that is characterized clinically by frequent presentation with obstructive jaundice, histologically by lymphoplasmacytic infiltrate and storiform fibrosis, and therapeutically by a dramatic response to steroids. When so defined, AIP has 2 subtypes, type 1 and type 2.

Type 1 AIP is considered the pancreatic manifestation of a multiorgan fibroinflammatory syndrome known as IgG4-related disease. This syndrome affects not only the pancreas but also various other organs, including the bile duct, salivary glands, retroperitoneum, and lymph nodes. Type 1 AIP is a disease of older men. Serum IgG4 levels are often elevated in type 1 AIP, and organs affected by AIP have a lymphoplasmacytic infiltrate that is rich in IgG4-positive cells. In type 1 AIP, the pancreas has a typical histologic pattern called *lymphoplasmacytic sclerosing pancreatitis*, characterized by a dense lymphoplasmacytic infiltrate around medium-sized ducts, a peculiar swirling (storiform) fibrosis, and an intense inflammation that surrounds veins (obliterative phlebitis) and spares adjacent arteries.

Most commonly, patients presenting with this form of chronic pancreatitis have obstructive jaundice that mimics pancreatic cancer; they rarely present with clinically acute or painful chronic pancreatitis. Pancreatic calcification is not common in AIP. The inflammatory process in type 1 AIP responds to corticosteroid therapy, although relapse is common after withdrawal of treatment. Many patients require long-term immunosuppression with either a low dose of corticosteroids or steroid-sparing agents such as azathioprine, 6-mercaptopurine, or mycophenolate mofetil.

Type 2 AIP occurs in younger patients and appears to be a pancreas-specific disorder. It is not associated with either serum IgG4 elevation or tissue infiltration with IgG4-positive cells. About 15% to 30% of patients with type 2 AIP have inflammatory

bowel disease. Histologically, type 2 AIP is characterized by neutrophilic infiltrate in the pancreatic duct epithelium (ie, a granulocyte epithelial lesion), which can lead to ductal obliteration. Type 2 AIP also responds to steroid therapy, but recurrences are far less common than in type 1 AIP.

The rest of the discussion in this chapter is related to chronic calcifying pancreatitis.

Etiology

Several conditions are associated with chronic calcifying pancreatitis (Table 37.1). The pathogenesis of chronic pancreatitis due to these presumed etiologic agents is largely unknown. However, clinical acute pancreatitis and the eventual development of chronic pancreatitis are currently thought to be due to the interaction between genetic and environmental factors. This applies not only to etiologic factors strongly associated with genetic mutations (eg, cationic trypsinogen gene mutations), but also to toxic-metabolic causes (eg, alcohol abuse). Six genes are associated with pancreatitis: cationic trypsinogen gene (*PRSS1*), anionic trypsinogen gene (*PRSS2*), serine protease inhibitor Kazal 1 gene (*SPINK1*), cystic fibrosis transmembrane conductance regulator gene (*CFTR*), chymotrypsinogen C gene (*CTRC*), and calcium-sensing receptor gene (*CASR*). Interactions between these and other unknown genetic factors and environmental, toxic, and metabolic factors (alcohol, smoking, hyperlipidemia, and hypercalcemia) are thought to lead to acute and chronic pancreatitis.

Table 37.1. Causes of Chronic Calcifying Pancreatitis (CP)

Presumed Cause	*Salient Features*
Alcohol	Most common cause of CP in the West
	CP develops in about 5% of alcoholic persons, usually after a long history of alcohol abuse
Hereditary	Mutations in the cationic trypsinogen gene (R117H, N21I) are associated with a high penetrance (80%) autosomal dominant form of CP
	Patients present at an early age (first and second decades)
	High risk of pancreatic cancer with time, especially for smokers
Tropical	Cause unknown
	Highest prevalence in South India
	Early age at onset (first and second decades)
	High prevalence (>80%) of diabetes mellitus and calcification at diagnosis
Idiopathic	Early (juvenile) and late (senile) forms
	Juvenile form is associated with mutations of the *CFTR* gene and *SPINK1* gene and with other mutations in the cationic trypsinogen gene, which are also associated with CP (probably as disease modifiers)
	Pain is a common feature of early-onset disease
	Senile form may be painless in about 50% of patients
Hypercalcemia	CP is an uncommon complication of hypercalcemia
Hypertriglyceridemia	Seen in children with disorders of lipid metabolism
	Associated with types I, II, and V hyperlipidemia
	Triglyceride levels >1,000 mg/dL

Diagnosis

Although histologic examination is the gold standard for diagnosis of chronic pancreatitis, it often is not available. Without histologic study, a combination of morphologic findings on imaging studies, functional abnormalities, and clinical findings is used to diagnose chronic pancreatitis. The diagnosis is relatively straightforward in the later stages of the disease when calcification and steatorrhea are present. The diagnosis is difficult when pancreatic structure and function are not unequivocally abnormal. Currently available diagnostic modalities are not adequate for making a firm diagnosis of chronic pancreatitis without obvious changes in structure and function.

Structural Evaluation

The imaging procedures commonly used to evaluate for structural changes in the pancreas are computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP). Pancreatic calcification suggestive but not diagnostic of chronic pancreatitis can be identified on abdominal radiographs. However, CT and EUS can detect small specks of calcifications not visible on plain radiographs.

Abdominal CT is a good first test for the evaluation of a patient who has possible chronic pancreatitis. It is noninvasive and widely available, with relatively good sensitivity for diagnosing moderate to severe chronic pancreatitis. The findings, however, can be normal in early chronic pancreatitis. Chronic pancreatitis is diagnosed with CT by the identification of pathognomonic calcifications within the main pancreatic duct or parenchyma or calcification within the dilated main pancreatic duct in combination with parenchymal atrophy. CT is also suitable for the evaluation of pain in a patient with known chronic pancreatitis, because most complications of chronic pancreatitis, including peripancreatic fluid collections, bile duct obstruction, and bowel obstruction, can be identified and inflammatory or neoplastic masses larger than 1 cm can be visualized reliably.

In the absence of a tissue diagnosis, ERCP is quite sensitive and specific for diagnosing moderate to severe pancreatitis. Pancreatic ductal changes seen on ERCP in chronic pancreatitis are listed in Table 37.2. Minor changes in the ducts are hard to interpret and are subject to interobserver variation. False-positive results may be obtained from older patients who may have benign pancreatic duct changes without pancreatitis and from patients with recent acute pancreatitis and reversible or permanent pancreatic duct changes in the absence of chronic pancreatitis.

Diagnostic ERCP carries a small risk (2%-5%) of causing complications, including pancreatitis. Therapeutic maneuvers have a higher risk of complication. ERCP is useful when other methods are nondiagnostic or unavailable, when patients have a clinical pattern of recurrent acute pancreatitis, or when a therapeutic intervention is being considered.

EUS provides high-resolution images of the pancreatic parenchyma and duct. Unlike ERCP, which can provide detailed images of changes in the pancreatic duct, EUS provides information about the pancreatic parenchyma as well as the duct. Nine ductal and parenchymal EUS features have been identified; the presence of more than 5 features strongly suggests the diagnosis of pancreatitis with structural abnormalities seen on other imaging studies. However, controversy remains regarding the diagnosis of "early" chronic pancreatitis (ie, chronic pancreatitis not evident on other imaging studies) based on EUS changes alone.

Table 37.2. Endoscopic Retrograde Cholangiopancreatography Grading of Chronic Pancreatitis (Cambridge Classification)

Grade	*Main Duct*	*Side Branches*	*Other Findings*
Normal	Normal	Normal	None
Mild	Normal	≥3 Abnormal	None
Moderate	Abnormal: dilated, strictures	≥3 Abnormal	None
Severe	Abnormal: dilated, strictures	≥3 Abnormal	>1 Finding: Large (>10 mm) cavity Intraductal filling defects or calculi Duct obstruction Severe duct dilatation or irregularities

There is significant interobserver disagreement on the presence or absence of EUS features and their interpretation. Problems with interpretation also may arise for older patients who have senile changes in the pancreas, for alcoholic patients in whom fibrosis may be present but not pancreatitis, and for patients who had a recent episode of acute pancreatitis. Currently, the diagnosis of chronic pancreatitis should not be based on EUS criteria alone.

MRCP is noninvasive, avoids the use of ionizing radiation and the administration of a contrast agent, and does not routinely require sedation, making it a diagnostic procedure of choice for some groups of patients. MRCP also avoids the risks associated with ERCP. In combination with conventional abdominal MRI, MRCP can provide comprehensive information about the pancreas and peripancreatic tissues. Major lesions such as grossly dilated ducts, communicating pseudocysts, and even pancreas divisum can be detected, but small duct changes and calcifications are not readily visualized. Also, the combination of MRI and MRCP does not have therapeutic potential.

Functional Testing in the Evaluation of Chronic Pancreatitis

The pancreas has great functional reserve, which means it must be damaged severely before functional loss is recognized clinically. For example, 90% of the pancreas has to be destroyed before steatorrhea occurs. Abnormal results of functional testing alone are not diagnostic of chronic pancreatitis, and diagnosis requires additional evidence of structural alteration seen on imaging studies consistent with chronic pancreatitis. Imaging studies by themselves usually are diagnostic by the time steatorrhea develops. Invasive tests of pancreatic function (eg, the "tubed" secretin test) show functional impairment even in the absence of steatorrhea. However, these tests are not widely available. Noninvasive tests of pancreatic function, such as fecal fat estimation, have poor sensitivity for the detection of early disease.

Clinical Features and Natural History

Abdominal pain is the dominant symptom in the early part of the natural history of chronic pancreatitis, and steatorrhea and diabetes mellitus are the prominent features of late, end-stage disease. Pain is often related to acute inflammatory flares. Some authors have reported a painless "burn out" of the pancreas in the late stages of the disease, but others have reported pain occurring even in late stages. Complications can occur after acute flares of pancreatitis or from chronic fibrosis in and around the pancreas.

The clinical features and natural history of chronic pancreatitis can differ remarkably in different forms of chronic pancreatitis. The age at onset of pain is much younger (first and second decades of life) in the hereditary and tropical forms of chronic pancreatitis. Although pain is a dominant feature of most forms of chronic pancreatitis, it may be absent in half the patients who have late-onset (senile) idiopathic chronic pancreatitis. Diabetes mellitus and calcification are uncommon at diagnosis in patients with alcoholic pancreatitis, but they are present at diagnosis in more than 80% of patients with tropical pancreatitis.

For patients with alcoholic chronic pancreatitis, death often is related to smoking and nonpancreatic and alcohol-related complications (especially cancers). For patients with tropical pancreatitis, the most common cause of death is diabetes-related complications, followed by pancreatic cancer. Pancreatic cancer can complicate any form of chronic pancreatitis, but it is especially common in the hereditary and tropical forms, probably because of the long duration of disease.

Complications

Diabetes Mellitus

Progressive decrease in islet cell mass leads to diabetes mellitus in chronic pancreatitis. Whereas diabetes is common at presentation in the tropical form of chronic pancreatitis, it is usually a late complication in other forms of the disease. Diabetes eventually develops in the majority of patients (85%), with or without resection, and nonresective surgery such as ductal drainage does not prevent it.

Steatorrhea

Steatorrhea occurs after more than 90% of the gland has been destroyed. Treatment involves oral pancreatic enzyme supplements. These are available as uncoated tablets or enteric-coated capsules or microspheres with pH-dependent release of enzymes. Patients with severe steatorrhea require 30,000 to 45,000 US Pharmacopeia units of lipase per meal and lesser amounts with snacks. Enzymes should be given with meals to allow proper mixing of food with the enzymes. Acid suppression may be required to prevent destruction of the enzymes by gastric acid. Fat-soluble vitamin levels should be measured at baseline and monitored periodically to correct any concomitant nutritional deficiencies.

Pseudocyst

In the early stages of the disease, pseudocysts are the result of a pancreatic duct leak following an attack of clinically acute pancreatitis. In later stages, ductal dilation can lead to leakage and the formation of pseudocyst from ductal "blowout." Upstream ductal obstruction due to stricture often results in the reformation of pseudocysts after simple enteral drainage (eg, endoscopic cyst drainage). This may require concomitant drainage of the main pancreatic duct (usually surgically) or resection of the diseased portion of the gland (or both).

Biliary Obstruction

Biliary obstruction could result from edema of the head of the gland following an acute attack, compression from a pseudocyst, bile duct entrapment in the fibrotic process involving the head of the gland, and complicating pancreatic malignancy in patients with long-standing disease. Edema of the head of the gland usually responds to conservative management, and compression of a pseudocyst responds to drainage of the pseudocyst. Fibrotic stricturing requires surgical biliary bypass. Pancreatic cancer complicating chronic pancreatitis can be difficult to diagnose early. Confirmed or suspected malignancy should be treated with resective surgery, if operable.

Duodenal Obstruction

Potentially reversible gastric outlet obstruction can occur during an acute flare of pancreatitis due to peripancreatic inflammation involving the gastroduodenal region. Nasojejunal feeding may be required to maintain nutrition during this period. Patients with a fibrotic process involving the duodenum require surgical bypass of the gastric outlet obstruction.

Splenic Vein Thrombosis

Because of the proximity of the splenic vein to the pancreas, the vein is often affected by pancreatic inflammation or fibrosis. Patients with left-sided portal hypertension (ie, sinistral portal hypertension) can present with gastric variceal bleeding, which is treated with splenectomy.

Management

Abdominal pain is the most dominant and vexing problem in the management of patients with chronic pancreatitis. It can vary in severity from mild, intermittent pain to severe, chronic, debilitating pain. In addition to the addiction to alcohol and tobacco that patients with alcoholic pancreatitis often have, there is also considerable potential for addiction to narcotics by those with severe pain. It is very difficult to assess the true severity of the pain of patients addicted to narcotics, and therapeutic interventions often are seemingly unsuccessful because of continued dependence on narcotics. Apart from these issues, a poor understanding of the pathogenesis of pain has made it difficult to rationally manage abdominal pain in patients with chronic pancreatitis. Despite some optimism that pancreatic pain eventually "burns out," most clinicians agree that the pain may diminish but rarely disappears with time.

A stepwise approach to pain management is recommended. However, the scientific evidence to support any of the measures taken (medical, endoscopic, or surgical) is scant, and there are very few well-defined prospective trials of therapy in comparison either with no therapy or with competing therapy.

An important first step is the assessment of a patient's pain and its nature, frequency, severity, and effect on quality of life and other activities. Patients who have intermittent (eg, episodes once a year or less), uncomplicated episodes with full function between episodes are probably better off without potentially injurious interventions. Regardless of the severity of pain, all patients with chronic pancreatitis should be counseled during each visit about abstinence from not only alcohol but also tobacco use.

Patients who have more significant, frequent, or severe pain and a tendency to take narcotics for pain control need further evaluation. The initial evaluation with imaging studies (eg, CT) should be undertaken to rule out complications of pancreatitis such as persistent acute inflammation (inflammatory mass) in the pancreas, pancreatic and peripancreatic fluid collections, biliary obstruction, and duodenal stenosis. Other diagnoses to be considered in the appropriate clinical context are peptic ulcer disease, gallbladder disease, and pancreatic cancer. The presence of any of these should lead to appropriate intervention.

In patients without the above conditions, medical, endoscopic, and surgical options have been attempted. Medical therapy includes a low-fat diet with abstinence from alcohol and use of high-dose pancreatic enzymes in association with acid suppression. Endoscopic therapy includes sphincterotomy, lithotripsy, and pancreatic duct stenting. Endoscopic interventions are appropriate before surgical therapy is considered except in patients with a heavy burden of stone disease, where surgery has been shown to result in better outcomes. Celiac plexus block, EUS-guided or percutaneous, appears to have limited benefit in chronic pancreatitis.

Surgical therapy is an option for patients who clearly appear to have disabling pancreas-related pain. The choice of operation, if elected, should be based on the morphology of the pancreatic duct. Treatment options include decompressive surgery, such as lateral pancreaticojejunostomy for patients with a dilated (>6 mm) pancreatic duct; partial pancreatic resection for those with a persistent inflammatory mass; or total pancreatectomy for patients with disease unresponsive to medical therapy and not suitable for other surgical options. A randomized controlled trial comparing pancreaticojejunostomy with endoscopic therapy for chronic pancreatitis with dilated ducts showed that surgery provided superior results, and a higher proportion of surgical patients reported pain relief. However, the 20% to 40% failure rate mentioned in even the most enthusiastic reports and the potential for surgical morbidity and mortality warrant reserving surgical treatment for patients who have severe pain not responsive to less invasive tactics.

Suggested Reading

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38

Pancreatic Neoplasms[a]

RANDALL K. PEARSON, MD

Pancreatic Ductal Adenocarcinoma

Almost uniformly, cancer of the pancreas is fatal and is increasingly a health problem. In the United States, the calculated incidence of pancreatic cancer in 2008 was 37,700, with 34,300 deaths due to the disease. The overall survival rate for persons with pancreatic cancer is less than 5%, the lowest 5-year survival rate with any cancer. This partly reflects the low resectability rate. Advanced age is the most common risk factor for pancreatic cancer, and as the population ages, the incidence of pancreatic cancer is predicted to increase.

Only 10% to 15% of patients are candidates for curative resection (stage I and stage II disease), and more than 50% have unresectable stage IV disease with distant metastases (Tables 38.1 and 38.2).

Risk Factors for Development of Pancreatic Cancer

Early diagnosis of pancreatic cancer is uncommon, and the tumor is detected most often at a late stage, when surgical resection is not possible. The causes of pancreatic cancer are unknown, and few environmental risk factors have been convincingly implicated.

Environmental Factors

Cigarette smoking is the most important risk factor and increases the relative risk by a factor of 1.5- to 3-fold. Furthermore, in hereditary pancreatic cancer kindreds, as well as in hereditary chronic pancreatitis, smoking lowers the age at onset of pancreatic cancer by 10 years. Persons working in the chemical, petrochemical, or rubber industries and hairdressers have a greater risk of pancreatic cancer, which may be related to exposure to aromatic amines.

Moderate intake of alcohol, high-fat diets, long-standing diabetes mellitus, coffee or caffeine intake, and use of aspirin have all been proposed to contribute to the risk of pancreatic cancer, but the evidence is limited or conflicting.

Hereditary Pancreatitis

Two mutations of the trypsinogen gene have been described in hereditary pancreatitis. There is a high incidence of pancreatic cancer among patients with hereditary pancreatitis, but this is probably related to the duration of chronic pancreatitis rather than specifically to the gene mutation. The estimated cumulative risk of pancreatic cancer at age 70 years is 40% (70- to 100-fold increased relative risk). Possibly in the future, methods will be available for identifying patients at risk for pancreatic cancer, but currently no established screening techniques have proven value.

Chronic Pancreatitis

According to a multinational study, patients with chronic pancreatitis have a cumulative risk of 2% per decade and a relative risk (the ratio of observed cases to expected cases) of 16 for pancreatic cancer. However, chronic pancreatitis is relatively uncommon and is not a major contributing factor in the population of patients with pancreatic cancer.

[a] Jonathan E. Clain, MD, is gratefully acknowledged as author of this chapter in the first edition of the book (parts of which appear in this edition).

Abbreviations: CA19-9, carbohydrate antigen 19-9; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; FOLFIRINOX, oxaliplatin, ironotecan, fluorouracil, and leucovorin; MPACT, Metastatic Pancreatic Adenocarcinoma Clinical Trial; MRI, magnetic resonance imaging

Table 38.1. Definition of TNM System for Staging of Pancreatic Ductal Adenocarcinoma[a]

Category	*Description*
	Primary Tumor (T)
TX	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	In situ carcinoma
T1	Tumor limited to pancreas; ≤2 cm in greatest dimension
T2	Tumor limited to pancreas; >2 cm in greatest dimension
T3	Tumor extends directly into any of the following: duodenum, bile duct, peripancreatic tissues, portal or superior mesenteric vessels
T4	Tumor extends directly into any of the following: stomach, spleen, colon, adjacent large arterial vessels
	Regional Lymph Nodes (N)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
	Distant Metastasis (M)
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

[a] Stages are defined in Table 38.2.

Intraductal Papillary Mucinous Tumors

Intraductal papillary mucinous tumors were recognized first in Japan in 1982 and increasingly are recognized in the United States. At Mayo Clinic, this condition has been identified in more than 100 patients. In about 25% to 50% of patients, invasive cancer is found at surgery (in some patients, it is not suspected preoperatively). Therefore, intraductal papillary mucinous tumor is a premalignant lesion, and surgical excision at presentation is the treatment of choice. (See Cystic Pancreatic Tumors section below.)

Diabetes Mellitus

More than 50% of patients who present with pancreatic cancer have diabetes mellitus, and in most patients, diabetes is diagnosed within 2 years of the diagnosis of cancer. Some but not all the patients are insulin-dependent, and in some, diabetes is diagnosed at the same time as pancreatic cancer. The development of diabetes mellitus appears to be due to an insulin resistance state induced by the cancer; cases of reversal of diabetes after Whipple resection have been reported. The precise risk of pancreatic cancer in patients with new-onset diabetes is not well defined.

Table 38.2. Stage Grouping for Pancreatic Ductal Adenocarcinoma[a]

Stage	*T*	*N*	*M*
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
II	T3	N0	M0
III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

[a] TNM staging system is defined in Table 38.1.

Inheritance

The evidence is consistent that 6% to 8% of patients who present with pancreatic cancer have a family history of pancreatic cancer in a first-degree relative. Families with 2 or more first-degree relatives with pancreatic cancer have an increased relative risk of 18- to 57-fold, depending on the number and ages of the relatives affected. Also, well-defined syndromes are associated with an increased incidence of pancreatic cancer, including Peutz-Jeghers syndrome (*STK11* mutations), hereditary nonpolyposis colorectal cancer (mismatch repair gene mutations), and familial atypical multiple mole–melanoma syndrome (mutations affecting p16). Rare kindreds have been identified in whom pancreatic cancer appears to be inherited in an autosomal dominant manner. Germline *BRCA2* mutations account for approximately 20% of these families and currently are the most common known inherited predisposition to pancreatic cancer.

It is not known at what age screening should begin or indeed whether any screening technique can detect early pancreatic cancer or improve prognosis. General guidelines include performing contrast-enhanced multidetector computed tomography (CT) or endoscopic ultrasonography at regular intervals, but there are no data to support this recommendation. Tumor markers, including K-*ras* and carbohydrate antigen 19-9 (CA19-9), are too insensitive and nonspecific.

Pathology

About 70% of pancreatic ductal adenocarcinomas occur in the head of the pancreas. Histologically, the neoplasms may vary from well-differentiated tumors that exhibit glandular structures in a dense stroma to poorly differentiated tumors that exhibit little or no glandular structure or stroma. Lymphatic spread appears to occur earlier than vascular invasion, which is present in more advanced lesions. Metastatic disease occurs mainly in the liver and lungs but also in the adrenals, kidneys, bone, brain, and skin.

Diagnosis

Patients with pancreatic cancer usually present with symptoms of pain, jaundice, weight loss (with or without anorexia), and early satiety. The most common symptom is abdominal pain, which occurs in up to 80% of patients. The presence of pain, particularly pain radiating through to the back, is associated with advanced lesions with a poor prognosis, the implication being that the tumor has spread beyond the pancreas.

Jaundice is the second most common presentation and occurs in about 50% of patients. For patients with cancer of the head of the pancreas, painless jaundice is the symptom most frequently predictive of resectability.

Overt steatorrhea is a far less common presenting symptom, even in patients with overt weight loss. When present alone, steatorrhea has been associated with longer survival. A small percentage of patients (approximately 5%) present with otherwise unexplained acute pancreatitis.

Tumor Markers for Diagnosis

Various tumor markers are increased in pancreatic cancer, but all lack sufficient sensitivity and specificity to be used as either diagnostic or screening tests. CA19-9 has the greatest sensitivity (about 70%) and specificity (about 87%) when the cutoff value is 70 U/mL. If a lower cutoff value is used, sensitivity is higher without much effect on specificity. However, the test is not useful

if the biliary tract is obstructed, because even benign biliary tract obstruction can cause a marked increase in CA19-9 levels. Approximately 5% to 10% of patients do not express Lewis antigens; thus, CA19-9 would not be detectable in this subgroup, further compromising the test for general screening. Also, CA19-9 levels are more likely to increase as the disease advances and becomes metastatic. For early-stage or resectable pancreatic cancer (stages I and II), the sensitivity of an increased CA19-9 value is reported to be as low as 50%, missing half the patients with disease at the stage appropriate for presymptomatic screening.

Genetic markers are present in patients with pancreatic cancer. The most common of these are the K-*ras* mutation in 90% of patients, *p53* tumor cell suppressor gene in 50% to 70%, and reduced expression of the *DCC* gene in about 50%. Other gene deletions are less common.

Although the K-*ras* mutation can be detected in pancreatic or duodenal juice or stool from patients with pancreatic cancer, it is present less frequently than in the tumor itself and, thus, is not a useful test because of low sensitivity. Furthermore, lack of specificity is an important issue because K-*ras* can be detected in patients with chronic pancreatitis.

Imaging Testing for Diagnosis

Multidetector CT with arterial and portal venous phase contrast enhancement ("pancreas protocol CT") should be the primary imaging study for the evaluation of patients with symptoms suggestive of pancreatic cancer. It is the appropriate study because not only is it diagnostic but it also can be used to stage the tumor. The increase in sensitivity (about 85%) of dual-phase multidetector CT is an important improvement over the ability of conventional CT (about 50%-60%) to diagnose pancreatic tumors. This sometimes leads to misconceptions about the role of dual-phase CT when researching the older literature about the importance of CT in diagnosis. For tumors smaller than 15 mm in diameter, however, the sensitivity of multidetector CT probably is still less than 80%.

Most studies support a role for endoscopic ultrasonography for a small cancer not detected with multidetector CT. The sensitivity of endoscopic ultrasonography for identifying a pancreatic mass is reported to be as high as 97%. Endoscopic ultrasonography has been described as the most accurate imaging test for diagnosing pancreatic cancer, being more accurate than transabdominal ultrasonography or CT. However, with the availability of multidetector CT with pancreas protocol contrast enhancement, the current role of endoscopic ultrasonography is in identifying small tumors and in performing fine-needle aspiration of the primary tumor or lymph nodes. Although endoscopic ultrasonographically guided fine-needle aspiration is a safe and effective method to diagnose pancreatic cancer, fine-needle aspiration is rarely performed at Mayo Clinic in patients with evidence of resectable pancreatic cancer because the results do not affect the clinical decision to proceed with surgery. Thus, the role for endoscopic ultrasonography fine-needle aspiration is limited mainly to patients with unresectable lesions, and whether it should be performed needs to be balanced against obtaining histologic material by percutaneous biopsy assisted by either ultrasonography or CT.

Staging Pancreatic Tumors

CT should be the initial test not only for diagnosis but also for staging of pancreatic cancer because it may provide evidence of distant metastases or clear vascular involvement, making further staging unnecessary (Figures 38.1 and 38.2). On

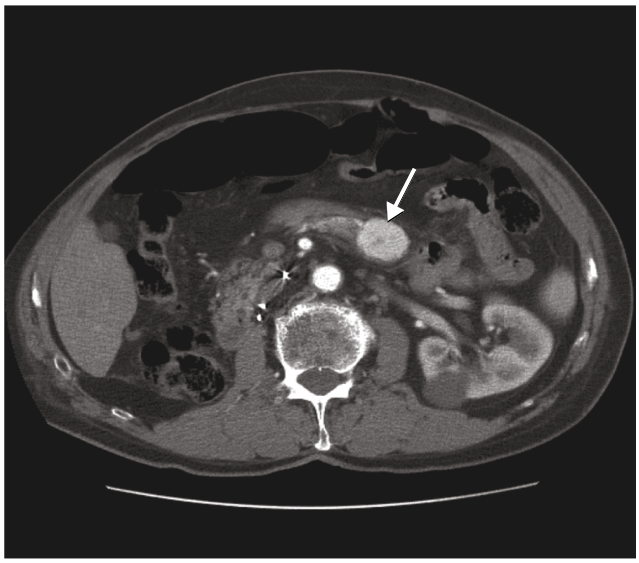

Figure 38.1. Hyperattenuating Lesion in Pancreas. Computed tomogram shows hyperattenuating lesion in the body of the pancreas (arrow). Primary pancreatic adenocarcinoma is usually hypoattenuating. This lesion would also be consistent with an islet cell tumor. The right kidney is absent. This lesion is a metastatic renal cell carcinoma.

contrast-enhanced multidetector CT images, ductal adenocarcinoma typically appears as an irregular, hypodense lesion. Magnetic resonance imaging (MRI) may be as accurate as multidetector CT, but generally it is not as readily available and there is not the same expertise in interpreting the findings. Endoscopic ultrasonography may be the most accurate method for staging local extent (T staging) (Figure 38.3) and nodal status (N staging). Correct interpretation of both CT and endoscopic ultrasonographic images regarding resectability varies depending on the study. For endoscopic ultrasonography, operator experience and the size of the tumor are important variables. Specifically,

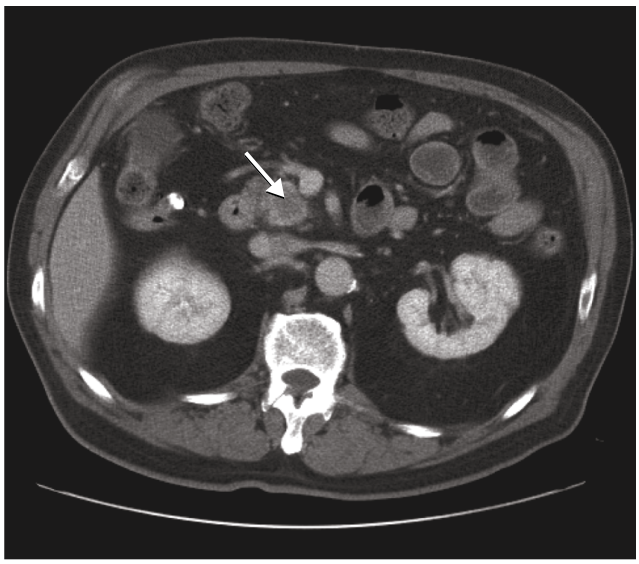

Figure 38.2. Pancreatic Cancer. Computed tomogram shows pancreatic cancer. A small hypoattenuating lesion is seen in the head of the pancreas (arrow). The superior mesenteric vessels are not involved by the tumor, which is resectable.

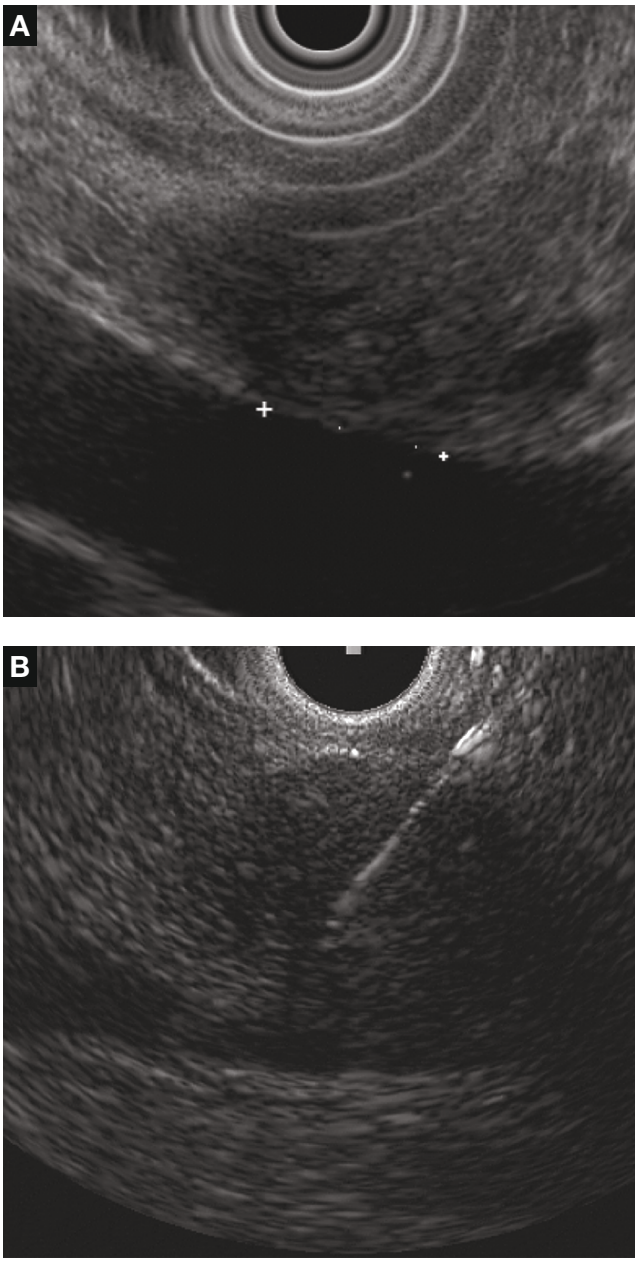

Figure 38.3. Hypoechoic Mass in Pancreas. A, Endoscopic ultrasonogram of the pancreatic head shows a poorly defined hypoechoic mass that impinges on the portal vein for a distance of 11 mm (indicated by 2 markers). Surgical resection confirmed invasion of the portal vein. B, Endoscopic ultrasonogram shows fine-needle aspiration of the mass shown in A.

the area of interest in relation to the vascular invasion requires imaging through the entire extent of the tumor, and with current equipment (either radial or curved linear scanning transducers), resolution progressively deteriorates with increasing depth of imaging. It is unclear whether advances in endoscopic ultrasonographic technology will improve its ability to determine resectability when CT (or MRI) findings are equivocal.

Small liver or peritoneal metastases usually are not seen on preoperative imaging studies. Some authors have recommended laparoscopy for viewing the liver and peritoneal surfaces preoperatively. About 10% to 15% of patients have these small metastases. Most centers do not routinely perform laparoscopy during preoperative assessment, but it can be argued that laparoscopy is indicated when the likelihood of unresectability is high. This would include all patients with cancer of the pancreatic body or tail, which has a very low chance of being resected and virtually no chance of cure, and patients with ascites, which usually is related to peritoneal metastases.

Treatment

Surgery

Most patients who undergo surgical resection for pancreatic cancer ultimately die of the disease, but the only chance of cure, albeit slim, is resection. For this reason, most major centers continue to endorse the surgical approach.

Preoperative biopsy or fine-needle aspiration of a pancreatic mass is not required in most instances because the findings do not alter the decision to resect. Of the patients who have the typical clinical presentation and preoperative imaging results, about 95% have pancreatic cancer confirmed at surgery. The other 5% usually have chronic pancreatitis, but it is not possible to confidently exclude tumor preoperatively. Thus, it is appropriate to perform a Whipple procedure. An important exception to this rule is autoimmune pancreatitis; this condition can mimic the presentation of pancreatic cancer and has characteristic clinical features that should alert astute clinicians preoperatively (see Chapter 37, "Chronic Pancreatitis"). In 10% to 15% of patients, pancreatic cancer may produce a desmoplastic response and tumor tissue may be difficult to procure with needle biopsy or fine-needle aspiration.

If surgical resection is not preceded by laparoscopy, the surgeon usually examines the peritoneal cavity and its contents carefully for obvious small metastases and then assesses vascular involvement, which requires mobilization of the tumor by dissection. The standard operation for pancreatic cancer is pancreaticoduodenectomy (Whipple procedure), which involves performing a cholecystectomy and removing a portion of the stomach (at least an antrectomy), the distal bile duct, the head of the pancreas, the duodenum, the proximal jejunum, and regional lymph nodes. Reconstruction with gastrojejunostomy, hepaticojejunostomy, and pancreaticojejunostomy is required. Results are good and mortality is low when the operation is performed by an experienced surgeon.

Alternative operations include a pylorus-preserving Whipple resection, which has become the surgical standard of care at most centers. This preserves the stomach and is a less extensive operation. It has been assumed that this operation, compared with the Whipple procedure, would improve outcome, especially long-term morbidity related to dumping syndrome and weight loss.

An extended or radical Whipple resection has been reported in the Japanese literature to provide better results, but these results have not been confirmed by studies in the United States or Europe; indeed, 4 prospective, randomized trials did not show an advantage for the more extensive procedure.

Surgery is the only chance for cure, but the median survival is only about 18 months and the 5-year survival rate is about 10%. Higher survival rates have been reported, and it appears that the different rates depend on tumor size (<2 cm), histologic grade, nodal status, and completeness of resection. For example, patients with tumors smaller than 2 cm have a reported 5-year survival rate of 20%, compared with only 1% for patients with tumors larger than 3 cm. The hypothesis that surgical treatment of early pancreatic cancer improves prognosis is based on these data.

At presentation, most patients have pancreatic cancer that is unresectable because of distant metastases or local extension. Because biliary obstruction can be relieved with endoscopic stenting, surgical management of biliary obstruction usually is limited to patients with a concomitant gastric outlet obstruction. Biliary diversion is achieved by cholecystenterostomy (but only when the cystic duct enters the common bile duct at a distance from the tumor) or by choledochoenterostomy. Because duodenal obstruction develops in less than 20% of patients before they die, it is the policy at nearly all centers not to perform prophylactic gastrojejunostomy. In some patients, neuropathy due to infiltration of the plexus by tumor, and not obstruction, may cause vomiting and slow gastric emptying; thus, a drainage procedure will not be helpful in these patients. Most patients who have jaundice and unresectable pancreatic cancer should have endoscopic stent placement. An expandable metal stent, rather than plastic, is the preferred endoscopic prosthesis for palliation because it is less likely to become occluded. This is especially true for patients with a life expectancy exceeding 3 months. Percutaneous transhepatic stenting has a lower success rate and a higher 30-day mortality rate and is not the procedure of choice. According to recent reports and the experience at Mayo Clinic, endoscopically placed expandable metal prostheses can successfully alleviate gastric outlet or duodenal malignant obstruction, but these new procedures require further evaluation before they can be recommended for routine use.

Palliation of pain is a major problem in patients with pancreatic cancer. Chemical intraoperative splanchnicectomy or celiac plexus block performed percutaneously or with endoscopic ultrasonography reportedly has reduced pain markedly. The advantage of plexus block is that it produces fewer complications related to narcotic use, namely, constipation, nausea, and vomiting. However, a randomized controlled trial that compared percutaneous celiac block with oral pharmacologic therapy showed no difference in survival. Still, there was improved control of pain with less narcotic use, especially shortly after the nerve block.

If oral analgesia is used to control pancreatic cancer pain, the type and dose of medication should depend on the severity of pain. For example, mild pain may be controlled with a combination of acetaminophen (325 mg) and oxycodone (5 mg), 1 or 2 tablets every 4 to 6 hours, whereas more severe pain may require a slow-release morphine compound, usually starting at a dose of 30 mg twice daily and increasing to a dose as high as 600 mg twice daily to achieve control. A short-acting liquid morphine compound may be useful to control breakthrough pain. Alternatively, a fentanyl (Duragesic) patch, 25 to 100 mg hourly, is effective for some patients.

Exocrine Pancreatic Insufficiency

Patients with cancer of the pancreatic head who have weight loss and stools suggestive of malabsorption should receive treatment with pancreatic enzymes. Available data suggest that pancreatic steatorrhea can be corrected with pancreatic replacement therapy.

Chemotherapy

Until recently, single-agent gemcitabine was the reference regimen for advanced metastatic pancreatic cancer, with published median survival ranging from 5 to 7 months. In 2011, a substantial advance was made with the results of a multicenter European trial that used a combination chemotherapy regimen of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX). Compared with single-agent gemcitabine, FOLFIRINOX resulted in a better objective response rate (32% vs 9%) and an overall survival that was nearly doubled (11.1 months vs 6.8 months). As expected with a multidrug regimen, toxicity was higher (especially neutropenia). For patients with excellent performance status and normal or nearly normal liver function, FOLFIRINOX will likely become the reference standard for advanced pancreatic cancer therapy.

An alternative, less toxic strategy combines gemcitabine with nanoparticle-coupled paclitaxel. Similar response rates (23%) and median survival advantages (8.5 months vs 6.5 months) over single-agent therapy were observed in the recently completed multinational Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT).

Therefore, management options for advanced pancreatic cancer may be finally changing for the better. These combination chemotherapy regimens are now being tested in locally advanced pancreatic cancer and in postsurgical adjuvant settings where single-agent fluorouracil and external beam radiotherapy have been the first-line therapy.

Cystic Pancreatic Tumors

Serous Cystadenoma

Classically, on presentation, serous cystadenomas are described as large, sometimes palpable, asymptomatic upper abdominal masses, but they frequently are small lesions in the head, body, or tail of the pancreas that are discovered incidentally on imaging studies (Figure 38.4). They occur equally in male and female patients and constitute up to 10% of all cystic lesions of the pancreas. Histologically, the tumors consist of multiple tiny cysts that contain watery fluid. When observed on imaging studies, the grapelike clustering of small cysts led to the use of *microscopic* to describe serous cystadenomas. Their cut surface shows a typical stellate scar (which is also evident on imaging). The malignant potential is almost zero (only a few case reports of malignancy have been published), and in elderly asymptomatic patients, these tumors frequently are only observed.

Mucinous Cystadenoma and Cystadenocarcinoma

Mucinous cystadenoma and cystadenocarcinoma occur almost exclusively in women 40 to 60 years old. They account for 1% to 2% of all pancreatic exocrine tumors. Foci of malignancy in many of the cysts and reports of patients with ostensibly benign resected cystadenomas later presenting with metastatic disease have led to the concept that these lesions have a moderate malignant potential. Recent surgical series have shown the importance of size: Mucinous cystadenomas smaller than 5 cm have a low potential for harboring invasive cancer. The tumors consist of multiple cysts (larger than those in serous cystadenomas and sometimes referred to as *macrocystic*) containing sticky mucus. As with serous cystadenomas, these lesions are often identified as a small cystic lesion in patients having CT for another reason.

Intraductal Papillary Mucinous Tumor

Intraductal papillary mucinous tumors, originally described in Japan, consist of intraductal papillary growth of mucin-producing columnar epithelium. These changes can occur in the main pancreatic duct or in side ducts and may involve a small portion of the pancreas or the entire gland. As a consequence of these changes, obstructive pancreatitis frequently occurs, with atrophy of the gland. Malignant transformation of the papillary growth

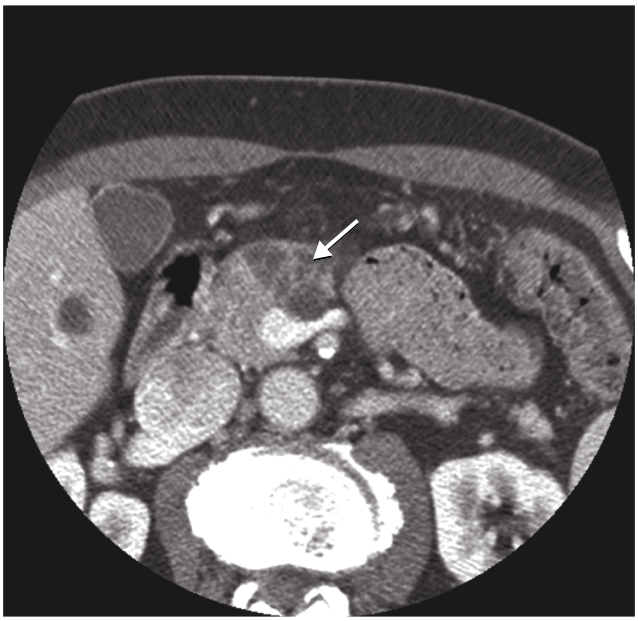

Figure 38.4. Serous Cystadenoma. Computed tomogram shows a serous cyst. The mass lesion in the head of the pancreas consists of multiple small cystic lesions (arrow). The findings are typical of serous cystadenoma.

has occurred in up to 30% to 50% of patients at the time of diagnosis, when the main pancreatic duct is involved. Because of this high rate of invasive cancer in main-duct intraductal papillary mucinous tumor, surgical resection is recommended. Early diagnosis is essential; once invasive cancer develops, half the patients will have local or distant metastases at the time of surgical resection. The malignant potential of side-branch intraductal papillary mucinous tumor appears to be much lower, and the long-term risk is unknown. Knowing when to recommend surgical resection (especially when a Whipple resection is required) is difficult.

Frequent clinical presentations include recurrent episodes of pancreatitis, abdominal pain, or steatorrhea. Jaundice and diabetes mellitus are less common. The diagnosis is suspected when a dilated pancreatic duct or side ducts are seen on CT. The chief differential diagnosis is chronic pancreatitis. At endoscopic retrograde cholangiopancreatography (ERCP), about half the patients have the diagnostic finding of a patulous papilla extruding mucus. Endoscopic ultrasonography may be helpful in making the diagnosis—and with less risk than ERCP. In addition, endoscopic ultrasonography can help exclude main-duct involvement and aid the clinician in assessing the risk of malignancy for the patient.

Solid-Cystic (Papillary-Cystic) Tumor

Solid-cystic tumor, which has various names, has a striking female predominance and usually occurs in adolescence. The histogenesis is unclear, but histologically, pseudopapillary and microcystic changes are seen. Most patients present with abdominal pain. Treatment of these often large tumors is excision. The prognosis is good, and most of the tumors can be considered benign, but occasionally metastatic disease occurs.

Approach to Small, Incidentally Observed Cystic Tumors of the Pancreas

When cystic tumors of the pancreas are small, CT and ultrasonography may not be able to resolve the nature of the cyst. The differential diagnosis includes benign congenital cysts, small pseudocysts, intraductal papillary mucinous tumor (especially branch duct), mucinous cystadenoma, serous cystadenoma, and degenerating endocrine or ductal adenocarcinomas. Endoscopic ultrasonography has an important role in defining its structure. For example, what may appear to be a unilocular simple cyst on CT may be seen on endoscopic ultrasonography to be a complex cyst with septations. Although aspiration of the cyst is a simple procedure, it is not clear whether analysis of the cystic fluid for carcinoembryonic antigen or mucin and cytologic examination for malignancy alter the decisions about management for most patients.

Generally, if the nature of a cyst cannot be determined precisely, the practice is to observe the cyst and to perform imaging studies at regular intervals to ensure that it is not rapidly increasing in size. Many of these incidentally found cysts meet the clinical and imaging criteria for branch-duct intraductal papillary mucinous tumor. A recently published international consensus on management recommended careful follow-up with imaging for asymptomatic peripheral cysts 3 cm or smaller.

Suggested Reading

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39

Gallstones[a]

FERGA C. GLEESON, MB, BCh

Autopsies performed on Egyptian and Chinese mummies demonstrate that gallstones afflicted humans more than 3,500 years ago. The prevalence of gallstones varies widely and is as high as 60% to 70% among American Indians and as low as 10% to 15% among white adults of developed countries. The prevalence is less among black Americans, East Asians, and people from sub-Saharan Africa. In the United States, gallstone disease is one of the most common and costly digestive diseases that requires hospitalization. The estimated annual direct cost is $6.2 billion. It is newly diagnosed in more than 1 million people annually, and approximately 700,000 cholecystectomies are performed each year. Therefore, an understanding of the anatomy and physiology, clinical presentation, and efficient approaches to investigations and management of gallstone disease are important. Optimal clinical management varies considerably, depending on the presentation.

[a] Portions of this chapter were adapted from Abou-Saif A, Al-Kawas FH. Complications of gallstone disease: Mirizzi syndrome, cholecystocholedochal fistula, and gallstone ileus. Am J Gastroenterol. 2002 Feb;97(2):249-54; Sonmez G, Ozturk E, Mutlu H, Sildiroglu O, Basekim C, Kizilkaya E. Education and imaging. Hepatobiliary and pancreatic: emphysematous cholecystitis. J Gastroenterol Hepatol. 2007 Nov;22(11):2035; and Attasaranya S, Fogel EL, Lehman GA. Choledocholithiasis, ascending cholangitis, and gallstone pancreatitis. Med Clin North Am. 2008 Jul;92(4):925-60. Used with permission.

Abbreviations: AST, aspartate aminotransferase; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HIDA, hepatobiliary iminodiacetic acid; MRCP, magnetic resonance cholangiopancreatography

Anatomy and Physiology

Gallbladder and Cystic Duct Anatomy

The gallbladder is a piriform sac situated primarily in the cystic fossa on the posteroinferior aspect of the right hepatic lobe. It develops from the cystic portion of the hepatic diverticulum. The neck of the gallbladder is connected to the cystic duct, which is 3 to 4 cm long, eventually joining the common hepatic duct to form the common bile duct. The cystic duct has 5 to 12 oblique folds that create the spiral Heister valve. The cystic artery, usually a branch from the right hepatic artery, courses superior to the cystic duct and reaches the superior aspect of the neck, where it divides into superficial and deep branches. Anatomical variations include gallbladder agenesis, multiple gallbladders, bilobed gallbladder, and double cystic duct. A phrygian cap is an inconsequential deformity reflecting kinking of the gallbladder fossa and is usually noted with radionuclide hepatobiliary imaging. In double gallbladder, each gallbladder may have its own cystic duct, or the duct may join to form a common cystic duct before joining the common hepatic duct.

Cholesterol Metabolism and Bile Acid Synthesis

The major components of bile are water and organic and inorganic solutes. The organic solutes include miscellaneous proteins, bilirubin, bile acids, and biliary lipids. Bilirubin is a degradation product of heme and usually is present as conjugated water-soluble diglucuronide. The unconjugated form of bilirubin precipitates, contributing to pigment or mixed cholesterol stones.

Bile acids are bipolar water-soluble molecules synthesized from cholesterol. When the level of bile acids is above the critical micellar concentration, bile acids self-associate to form micelles

capable of solubilizing hydrophobic lipid molecules in bile or intestinal chyme. The primary function of micelles is to facilitate fat digestion and absorption. The primary bile acids (cholic acid and chenodeoxycholic acid) are manufactured in the liver. They are converted to secondary bile acids (deoxycholic and lithocholic acids) by bacteria in the gut.

The major biliary lipids, cholesterol and lecithin (phospholipid), are insoluble in water. They are secreted into bile as lipid vesicles and are carried in both vesicles and mixed micelles.

In health, the gallbladder concentrates bile 10-fold for efficient storage during fasting and empties 25% of its contents every 2 hours. Intraduodenal protein and fat release cholecystokinin, which stimulates contraction of the gallbladder, relaxation of the sphincter of Oddi, and flow of bile to the intestine. More than 90% of bile acids are actively absorbed in the terminal ileum. This enterohepatic circulation cycles 4 to 12 times daily, slowing during fasting and accelerating greatly after a meal (Figure 39.1).

Gallstone Pathogenesis and Epidemiology

Gallstones are categorized on the basis of composition as *cholesterol gallstones* (80% of patients) and *pigment* (black and brown) *gallstones* (20%). Each category has a unique structural, epidemiologic, and risk factor profile (Table 39.1). Cholesterol crystal formation requires the presence of 1 or more of the following: cholesterol supersaturation, accelerated nucleation, or gallbladder hypomotility, bile stasis, and genetic factors.

Cholesterol gallstones contain a mixture of cholesterol (50%-99% by weight), a glycoprotein matrix, and small amounts of calcium and bilirubin. Cholesterol supersaturation can result from deficient secretion of bile acid or hypersecretion of cholesterol. Bile acid secretion may be diminished because of decreased synthesis, as occurs with older age or liver disease, or because of decreased enterohepatic circulation, as occurs with motor disorders, hormonal defects, and increased gastrointestinal losses from bile acid sequestrant therapy or terminal ileal disease, resection, or bypass. Cholesterol secretion increases with hormonal stimuli (female sex, pregnancy, exogenous estrogens, and progestins), obesity, hyperlipidemia, age, chronic liver disease, and sometimes with excessive dietary polyunsaturated fats or increased caloric intake. In a supersaturated environment, the initial formation of gallstone crystals results from an excess of nucleating effects compared with antinucleating effects of the various proteins in bile (Figure 39.2 and Box 39.1).

Gallbladder dysmotility results in inadequate clearance of crystals and nascent stones. Motility is decreased in the presence of supersaturated bile even before stone formation. Decreased motility is a dominant contributing factor to stone development during pregnancy, prolonged total parenteral nutrition, somatostatin therapy, or somatostatinoma.

The prevalence of cholesterol gallstones varies with geography and ethnicity. They are rare in populations of Africa and most of Asia, they are common in most Western populations (15%-20% of women, 5%-10% of men), and they occur almost uniformly in North and South American Indians (70%-90% of

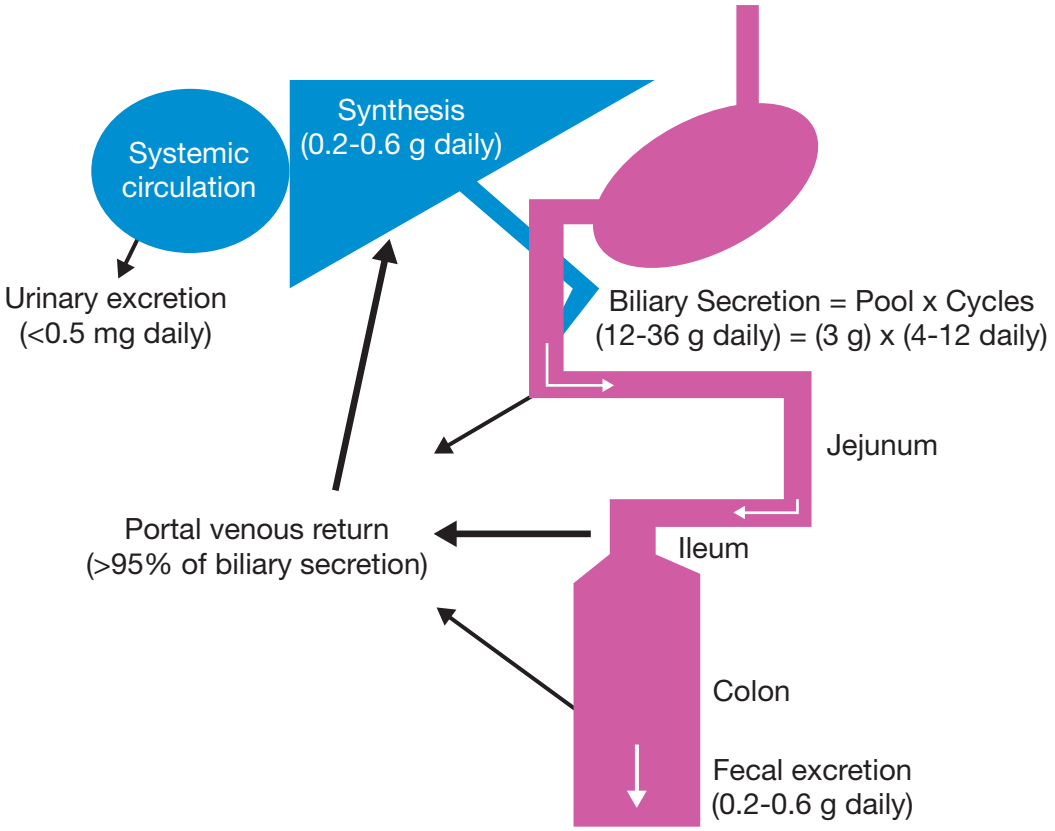

Figure 39.1. Enterohepatic Circulation. A pool of 3 g of bile acid cycles 4 to 12 times daily. Ileal absorption returns 97% of intraluminal bile acids to the circulation; 90% of bile acids are extracted from the portal system on their first pass through the liver. In health, hepatic synthesis of bile acids is equivalent to enteric losses. (Adapted from Zucker SD, Gollan JL. Physiology of the liver. In: Haubrich WS, Schaffner F, Berk JE, editors. Bockus gastroenterology. Vol 3. 5th ed. Philadelphia [PA]: WB Saunders Company; c1995. p. 1858-904. Used with permission.)

Table 39.1. Types of Stones: Characteristics and Clinical Association

Feature	*Cholesterol Gallstones*	*Black Pigment Gallstones*	*Brown Pigment Gallstones*
Composition	50%-99% cholesterol by weight	Calcium bilirubinate Calcium phosphate	Unconjugated bilirubin, palmitate sterate, cholesterol, and mucin
Color	Yellow-brown	Black	Brown
Consistency	Crystalline	Hard	Soft, greasy
Location	Gallbladder with or without common bile duct	Gallbladder with or without common bile duct	Bile ducts rather than gallbladder
Radiodensity	Lucent (85%)	Opaque (>50%)	Lucent (100%)
Bile culture	Sterile	Sterile	Infected (eg, *Escherichia coli*)
Recurrent stones	Rare	Rare	Frequent
Clinical associations	Increased gastrointestinal losses from bile acid sequestrant therapy Terminal ileal disease, resection, or bypass Hormonal stimuli (female sex, pregnancy, exogenous estrogens, and progestins) Obesity Hyperlipidemia Older age Chronic liver disease Excessive dietary polyunsaturated fats or caloric intake Pregnancy Prolonged total parenteral nutrition Somatostatin therapy Somatostatinoma	Chronic hematolytic states including sickle cell disease, mechanical heart valves Cirrhosis Gilbert syndrome Cystic fibrosis Total parenteral nutrition May have no identifiable cause	Proximal to biliary stricture Proximal to duodenal diverticulum Following sphincterotomy Biliary parasites

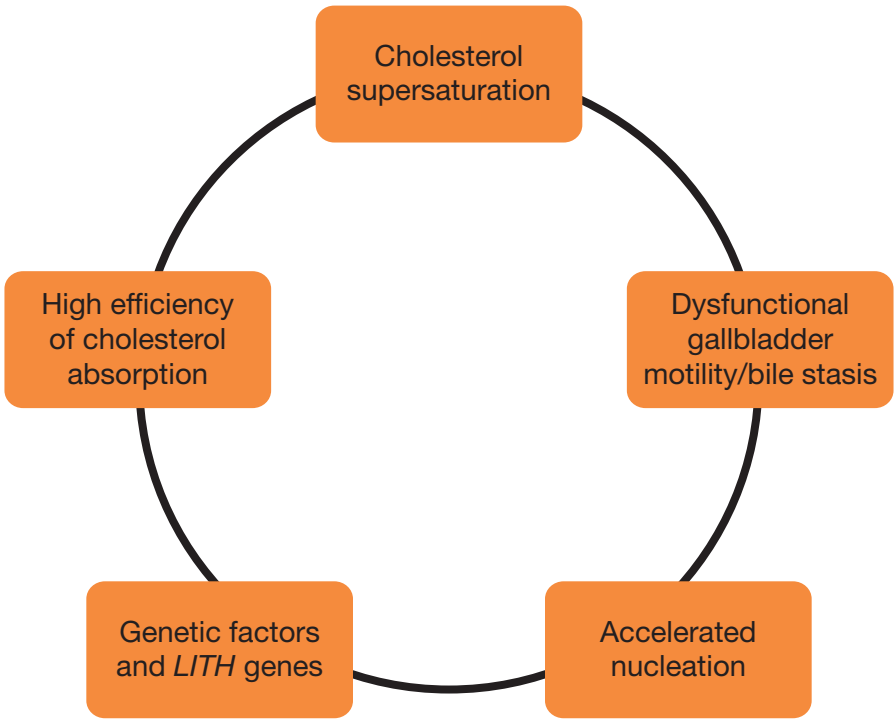

Figure 39.2. Defects Resulting in Gallstone Formation. Studies have shown that interactions of 5 defects result in nucleation and crystallization of cholesterol monohydrate crystals in bile, with eventual formation of gallstones.

Box 39.1. *LITH* Genes and Potential Mechanisms

ATP-binding cassette transporter B4: Biliary phospholipid secretion is decreased

β_3-Adrenergic receptor: Gallbladder hypomotility

Apolipoprotein A-I: Biliary cholesterol secretion is increased from an increase in reverse cholesterol transport

Apolipoprotein B: Biliary cholesterol secretion is increased from a decrease in hepatic VLDL synthesis and an increase in intestinal cholesterol absorption

Cholecystokinin 1 receptor: Gallbladder and small intestinal hypomotility

Cytochrome P450 7A1 isozyme: Bile salt synthesis is decreased

Estrogen receptor 2: Cholesterol synthesis is increased

Cholesterol ester transfer protein: Hepatic cholesterol uptake is increased from HDL catabolism

Abbreviations: ATP, adenosine triphosphate; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein.

women). For all populations, the prevalence increases with age and is approximately twice as high in women as in men.

Generally, pigment gallstones are formed by the precipitation of bilirubin in bile. Black pigment gallstones are formed in sterile gallbladder bile in association with chronic hemolytic states, cirrhosis, Gilbert syndrome, or cystic fibrosis, or they may have no identifiable cause. These stones are small, irregular, dense, and insoluble aggregates or polymers of calcium bilirubinate. Brown pigment gallstones occur primarily in the bile ducts, where they are related to stasis and chronic bacterial colonization, as may occur above strictures or duodenal diverticula, following sphincterotomy, or in association with biliary parasites. Brown pigment gallstones are composed of 10% to 30% cholesterol. They are softer than black pigment gallstones and may soften or disaggregate with cholesterol solvents.

Clinical Presentation and Complications

Cholelithiasis

Frequently, the diagnosis of asymptomatic cholelithiasis is the result of widespread use of abdominal ultrasonography to evaluate nonspecific abdominal symptoms. Approximately 10% to 20% of Western populations have cholelithiasis, and of these people, 50% to 70% are asymptomatic when cholelithiasis is initially identified. Commonly, asymptomatic disease has a benign course and the proportion of those with disease that evolves from asymptomatic to symptomatic is relatively low (10%-25%). When patients with gallstones eventually become symptomatic, only 2% to 3% present initially with acute cholecystitis or other complications. Asymptomatic stones generally do not require therapy.

Prophylactic cholecystectomy should be considered, however, for patients who are planning extensive travel in remote areas and for American Indian populations, in whom the relative risk for stone-associated gallbladder carcinoma is 20 times higher than for those without stones. Patients with midgut carcinoid tumors are commonly treated with somatostatin analogues. The adverse effects of these analogues include impairment of gallbladder function, formation of gallstones, and cholecystitis. Therefore, prophylactic cholecystectomy may be beneficial for this cohort of patients. Concomitant cholecystectomy at the time of a Roux-en-Y gastric bypass for ultrasound-confirmed gallbladder pathology is feasible and safe and may reduce the potential for future gallbladder-related morbidity. A similar rationale may be used when prophylactic splenectomy is performed in patients with hereditary spherocytosis. Cholecystectomy is not recommended for asymptomatic patients who have stones and diabetes mellitus or sickle cell disease if they have access to medical care. Progressive gallstone dissolution by oral litholysis with hydrophilic ursodiol may be attempted in patients who have mild symptoms and small, uncalcified cholesterol gallstones in a functioning gallbladder with a patent cystic duct. Daily ursodiol may reduce the frequency of gallstone formation in obese patients eating low-calorie diets.

Biliary colic is a relatively specific form of pain secondary to increased intragallbladder pressure due to hormonal or neural stimulation. This may be triggered by a fatty meal or a stone compressed against the gallbladder outlet or cystic duct opening. The pain usually develops rapidly in the epigastrium or right upper quadrant and lasts longer than 15 minutes but not longer than 4 to 6 hours. The likelihood of patients experiencing a severe event or complication is approximately 1% per year, prompting the recommendation of surgical therapy for symptomatic gallstones. Histologically, most patients with recurrent biliary colic have chronic cholecystitis.

Cholecystitis is a syndrome that encompasses a continuum of clinicopathologic states. One end of this continuum is chronic cholecystitis, with intermittent episodes of biliary colic. The other end is acute cholecystitis, with abdominal pain that lasts longer and is accompanied by fever, leukocytosis, or cholestasis. Acute cholecystitis is associated with age older than 60 years, male sex, diabetes mellitus, history of cardiovascular disease, and a history of cerebrovascular accident. In an immune-compromised patient, it may be related to cytomegalovirus or *Cryptosporidium* infections. The most common complication is gangrene of the gallbladder (20%), and therefore, early cholecystectomy is recommended for patients who have symptomatic cholelithiasis and these adverse risk factors. However, cholecystectomy is not indicated for patients who have isolated abnormal results on liver biochemical tests or cholestasis in the absence of choledocholithiasis.

Acute acalculous cholecystitis accounts for 6% to 17% of all acute episodes and is associated with a high mortality rate and is difficult to diagnose. It generally occurs in acutely ill, hospitalized patients. It also may develop postoperatively and in critically ill patients and may be complicated by the development of gangrene, perforation, and empyema. Diabetes mellitus, malignant disease, abdominal vasculitis, congestive heart failure, cholesterol embolization, shock, and cardiac arrest also have been associated with acute acalculous cholecystitis. The overall mortality rate is 50%. Ultrasonography, computed tomography (CT), and hepatobiliary iminodiacetic acid (HIDA) scans are the most useful imaging examinations. Diagnostic laparoscopy and, potentially, laparotomy have been recommended by the Society of American Gastrointestinal and Endoscopic Surgeons for acute acalculous cholecystitis.

Between 5% and 40% of all laparoscopic cholecystectomy procedures are associated with spillage of gallstones. Gallstones

also may be dropped during open cholecystectomy, but the larger operating field makes them easier to retrieve. Dropped gallstones may mimic colon cancer, liver abscess, subphrenic abscess, peritoneal metastases, and intra-abdominal actinomycosis.

Gallbladder Polyps

Polypoid lesions of the gallbladder typically are incidental findings and represent any projection of mucosa into the gallbladder lumen regardless of neoplastic potential. The majority are benign nonneoplastic lesions that include cholesterol polyps (usually pedunculated), adenomyomatosis, and inflammatory polyps. Cholesterol polyps are usually smaller than 10 mm in diameter and appear on ultrasonography as tiny echogenic spots or echogenic pedunculated masses without acoustic shadowing. Gallbladder polyps can also develop in patients with a congenital polyposis syndrome such as Peutz-Jeghers syndrome or Gardner syndrome. Solitary sessile polyps larger than 10 mm in diameter in patients older than 50 years should be considered for cholecystectomy, as should polyps in patients who have cholelithiasis or primary sclerosing cholangitis.

Gallstones and Pregnancy

Symptomatic gallstone disease is the second most common abdominal emergency in pregnant women. Insulin resistance is a risk factor for incidental gallbladder sludge and stones during pregnancy, even after adjustment for body mass index. Insulin resistance may represent a causal link between obesity and gallstones. In addition, the pregnant state impairs gallbladder motility and increases biliary cholesterol saturation. Endoscopic retrograde cholangiopancreatography (ERCP) can be performed safely during pregnancy but may be associated with an increased rate of post-ERCP pancreatitis compared with the rate for the general population. Studies that compared conservative management with surgical management of cholecystitis showed no significant difference in the incidence of preterm delivery or fetal mortality. Laparoscopic cholecystectomy is safe in all trimesters. In 12 reports of gallstone pancreatitis, the fetal mortality rate was 8% for the conservative management group and 2.6% for the surgical management group, suggesting the need for earlier surgical intervention. Hospitalization for gallstone-related disease is common in the first postpartum year, most often for uncomplicated cholelithiasis. Risk factors for hospitalization include elevated prepregnancy body mass index, Latino ethnicity, and older maternal age.

Microlithiasis and Sludge

Microliths are a component of biliary sludge, consisting of relatively larger particles (1-3 mm) that are an essential step in the development of gallstones. Microscopic examination of bile under polarized light can detect cholesterol crystals, which are a surrogate marker for biliary sludge and gallstones. The chemical composition of sludge includes cholesterol monohydrate crystals, calcium bilirubinate granules, calcium phosphate and calcium carbonate crystals, and calcium salts of fatty acids; the composition of sludge correlates well with the composition of stones. A higher prevalence of detectable gallbladder sludge is noted during pregnancy, total parenteral nutrition (secondary to gallbladder stasis), weight loss, prolonged fasting, and prolonged treatment with octreotide and following the intravenous administration of ceftriaxone.

Biliary sludge or microlithiasis may cause acalculous biliary pain and may obstruct the common bile duct, manifesting as acute cholangitis or pancreatitis. Consequently, occult microlithiasis should be suspected when patients have acute pancreatitis of unknown origin, particularly if relapses are frequent. It is a well-recognized complication following liver transplant; in 6% of patients, cholangiography shows biliary filling defects ultimately attributed to sludge-cast, gallstones, or necrotic debris. The formation of biliary sludge is a serious, life-threatening complication. Biliary strictures and prestenotic dilatations of the bile ducts are the major reasons for sludge formation.

Expectant management is warranted for incidentally detected asymptomatic sludge. Similar to that for overt gallstone disease, treatment is necessary only if patients are symptomatic or have complications. Endoscopic sphincterotomy with either ursodiol treatment or laparoscopic cholecystectomy is a useful alternative for patients who have biliary sludge and recurrent obstruction of biliary outflow associated with recurrent cholangitis or pancreatitis. After liver transplant, biliary sludge should be treated endoscopically.

Choledocholithiasis

Choledocholithiasis (ie, stones in the common bile duct) should be suspected in patients who have symptomatic cholelithiasis or acute biliary pancreatitis and possibly in patients who have had cholecystectomy. Choledocholithiasis occurs in 10% to 15% of people who have cholelithiasis. Concomitant cholelithiasis and choledocholithiasis occur more frequently in elderly Asian patients, in patients with chronic bile duct inflammation (sclerosing cholangitis or parasitic infestation), and in patients with hypothyroidism. A common bile duct stone detected on ultrasonography is the most reliable predictor of such stones at ERCP or surgery. The specificity of ultrasonography for common bile duct stones is high (Figure 39.3). Combination therapy consisting of endoscopic biliary sphincterotomy and biliary drainage as initial treatment for patients with moderate acute cholangitis is safe and should not prolong hospitalization. Extracorporeal shock wave lithotripsy of duct stones is clinically approved and feasible, although infrequently used. It is coupled with ERCP for the removal of stone debris.

Bile duct stones recur in 4% to 24% of patients during follow-up. They may recur after cholecystectomy. This is thought to be due to bile stasis and bacterobilia. A small amount of postcholecystectomy syndromes (in symptomatic postcholecystectomy patients) are related to a residual stone in a particularly long cystic duct or to the relapse of lithiasis in a gallbladder remnant. Common bile duct dilation (≥13 mm) and the presence of a periampullary diverticulum are risk factors for recurrent stones.

Ascending Cholangitis

Acute cholangitis, or biliary tree infection, occurs as a consequence of biliary tract obstruction that promotes bile stasis and bacterial growth. Bacteria ascending from the duodenum are the main bacterial entry route. Secondary and less frequent routes of entry are the portal venous system and the periportal lymphatic system. Most episodes are due to coliforms such as *Escherichia coli, Klebsiella* (70% of cases), *Enterococcus, Pseudomonas*, and anaerobes (*Clostridium* and *Bacteroides*) (10%-15% of cases). The occurrence of bacteremia or endotoxemia correlates directly with intrabiliary pressure.

Common bile duct stones are the most common cause, and the presentation may range from a mild, self-limited process to

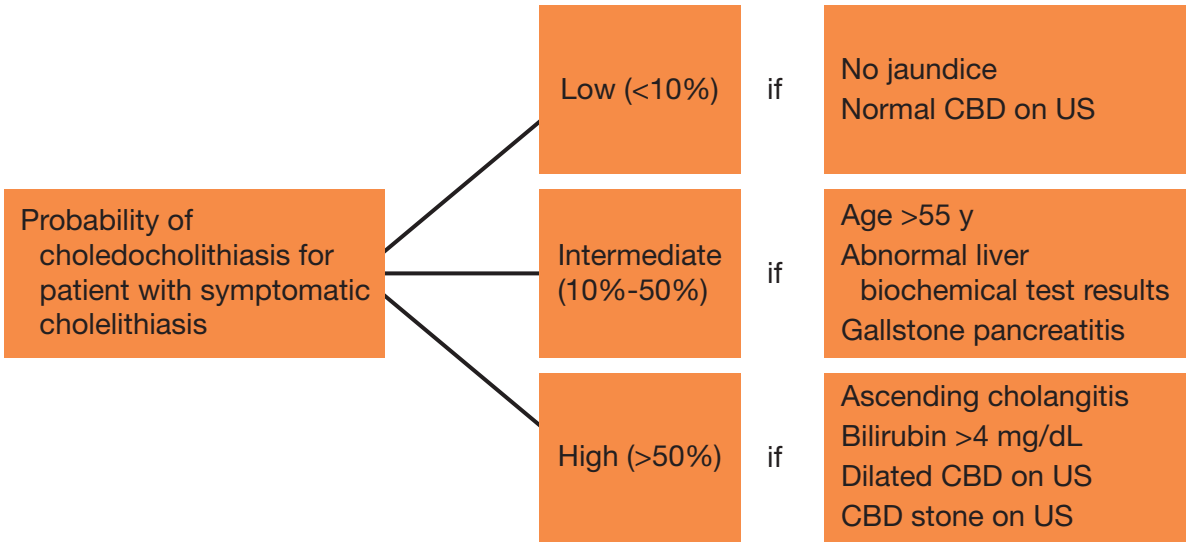

Figure 39.3. Probability of Choledocholithiasis. The probability of common bile duct stones is based on clinical, laboratory, and ultrasonographic variables. CBD indicates common bile duct; US, ultrasonography.

a serious, life-threatening condition that requires intervention. It also may be due to a biliary stricture from a previous biliary operation, liver transplant, primary sclerosing cholangitis, or acquired immunodeficiency syndrome–related cholangiopathy. In 1877, Charcot described a triad of fever, right upper quadrant pain, and jaundice; this triad occurs in 56% to 70% of patients who have cholangitis. The Reynolds pentad, which includes hypotension and alteration of consciousness in addition to the features of the Charcot triad, is seen less frequently (5%-7% of cases).

Initial therapy should include the empirical use of broad-spectrum antibiotics with adequate biliary excretion. Useful antibiotics include ampicillin-sulbactam, piperacillin-tazobactam, third- or fourth-generation cephalosporins, quinolones, and carbapenems. Ceftriaxone is associated with the appearance of biliary sludge due to calcium salt precipitation, but the sludge should dissipate spontaneously once use of the drug is discontinued. Elderly patients, patients with a biliary stent in situ, or those who had previous enterobiliary surgery may benefit from additional enterococcal and anaerobic antimicrobial coverage. The timing of biliary decompression depends on the initial response to antibiotics, and supportive care can be provided by endoscopic, percutaneous, or surgical approaches or by multimodal therapy. ERCP with nasobiliary drain placement, stent, or endoscopic sphincterotomy and common bile duct clearance is associated with considerably lower morbidity and mortality than traditional surgical management. If endoscopy does not allow access, subsequent percutaneous or surgical decompression should be pursued, depending on the clinical urgency.

Patients with recurrent pyogenic cholangitis (also called Oriental cholangiohepatitis) present with recurrent, progressively severe, and frequent attacks of cholangitis with associated extensive stone disease, especially of the intrahepatic ducts. Secondary duct dilatation, stricture formation, and further stone formation become self-perpetuating. This form of cholangitis occurs especially in the Asian-Pacific basin. The pathogenetic mechanism is not understood completely; however, postulated causes include primary congenital biliary strictures and cysts, biliary parasitic infection (*Ascaris lumbricoides, Opisthorchis* species, or *Opisthorchis sinensis* [also known as Chinese liver fluke]), and chronic intrahepatic bacterial colonization from unclear sources. Ascaris infection is also associated with intrahepatic gallstones. Therapy is directed at duct decompression, drainage, stone clearance, and, occasionally, lobar or segmental resection for isolated intrahepatic disease. Isolated unilateral intrahepatic involvement is most common in the left hepatic ductal system.

Sump syndrome can occur in patients after choledochoduodenostomy if debris (mainly food) accumulates in segments of the native biliary tree. This results in pain and cholangitis, requiring native papilla sphincterotomy.

Functional Gallbladder Disorder (Gallbladder Dyskinesia)

Functional gallbladder disorder is characterized by biliary-like pain in patients who have an ultrasonographically normal gallbladder. Synonyms include *gallbladder dyskinesia, chronic acalculous gallbladder dysfunction, acalculous biliary disease*, and *biliary dyskinesia* (Box 39.2). The estimated prevalence is 8% for men and 21% for women, but the pathogenesis is poorly understood. Even though evidence-based recommendations cannot be made, the use of a neuromodulator is reasonable for patients with suspected functional gallbladder disorder. Anticholinergic drugs and narcotics are associated with impaired gallbladder emptying. If symptoms persist, oral cholecystography should be performed with and without cholecystokinin stimulation and with measurement of the gallbladder ejection fraction (a quantitative measurement of gallbladder emptying). This is the most frequently used investigation to evaluate functional gallbladder disorder. If the ejection fraction is less than 35%, cholecystectomy should be considered—but only for patients with classic biliary symptoms.

Gallstone Complications

The incidence of *gallstone pancreatitis* is increased for women older than 60 years. The pathogenesis is thought to be related to increased pressure within the pancreatic duct, with biliopancreatic reflux, due to passage of a common bile duct stone or an impacted stone at the level of the papilla. Suspicion of acute gallstone pancreatitis is increased if patients have acute pancreatitis associated with abnormal results from liver function tests, evidence of

Box 39.2. Rome III Criteria for the Diagnosis of Functional Gallbladder Disorder

Episodes of pain in the upper quadrant or epigastrium and all of the following:

- Gallbladder in situ
- Normal liver chemistry values and normal amylase and lipase levels
- Duration of pain ≥30 min
- Recurrent episodes occur at different intervals (not daily)
- Pain builds up to a steady level
- Pain is severe enough to interrupt the patient's current activities or lead to a visit to a clinician or emergency department
- Pain is not relieved by bowel movements, postural change, or antacids
- Other structural diseases have been excluded

Adapted from Appendix A: Rome III criteria for the diagnosis of functional gastrointestinal disorders, section E [Internet]. Raleigh (NC): Rome Foundation, Inc; c2013 [cited 2014 Apr 4]. Available from: http://www.romecriteria.org/assets/pdf/19_RomeIII_apA_885-898.pdf. Used with permission.

cholelithiasis, or biliary tree dilatation. Transabdominal ultrasonography is the most cost-effective initial investigation to document the presence of cholelithiasis, with or without common bile duct dilatation. Bowel gas and stones smaller than 4 mm may reduce the overall sensitivity. Pancreatic parenchymal and peripancreatic inflammatory changes are best detected and evaluated with contrast-enhanced CT, which also may show pancreatic neoplasm, pancreatic calcification, or choledocholithiasis. Because patients have a high risk of recurrence within 30 days after an attack, they should undergo cholecystectomy during the index hospitalization, after their symptoms have resolved.

Gallstone ileus is a disease of the elderly, with a female predominance. It frequently is preceded by an episode of acute cholecystitis. The resulting obstruction is a true mechanical phenomenon; therefore, the term *ileus* is a misnomer. The cholecystitis-related inflammation and adhesions facilitate the erosion of the offending gallstone through the gallbladder wall, forming a cholecystoenteric fistula and facilitating stone passage. The duodenal wall is the most common fistula site, but it may occur anywhere in the gastrointestinal tract (colon, stomach, and small bowel). An iatrogenic fistula can form after endoscopic sphincterotomy or a surgical choledochoduodenostomy. A stone smaller than 2 to 2.5 cm usually passes spontaneously through a normal gastrointestinal tract. Stones larger than 5 cm are more likely to become impacted. The terminal ileum and ileocecal valve are the most common locations because of the relatively narrow lumen and decreased peristalsis. Presenting symptoms may be intermittent, because the passing stone may lodge at various levels of the bowel. A passing stone is responsible for 25% of all bowel obstructions in patients older than 65 years, compared with 1% to 3% in all age groups. Abdominal radiography may show bowel obstruction, pneumobilia, and an abnormally located stone. CT may identify larger stones, evidence of bowel obstruction, and the level of obstruction. Surgical intervention is the treatment of choice for the majority of patients and may include biliary surgery when the intestinal obstruction is relieved.

Obstruction at the level of the gastric outlet by a gallstone is called *Bouveret syndrome*. It is an uncommon form of gallstone ileus. A single gallstone at least 2.5 cm in diameter is the most common underlying cause of this syndrome.

Mirizzi syndrome describes a common hepatic duct obstruction due to extrinsic compression from an impacted cystic duct stone. Patients present with a triad of fever, right upper quadrant pain, and jaundice, with elevations in bilirubin and alkaline phosphatase. They have an increased risk of gallbladder cancer. Mirizzi syndrome is noted in 0.7% to 1.4% of patients undergoing biliary surgery. In 11% of patients, the cystic duct courses parallel to the extrahepatic bile duct and inserts medially into it at the level of the papilla.

Emphysematous cholecystitis is a rare form of acute cholecystitis in which the gallbladder becomes infected with gas-forming organisms such as *Clostridium perfringens, E coli*, and *Klebsiella* species. Most patients are between 50 and 70 years old and, in contrast to typical patients with acute cholecystitis, men are more likely to be affected than women. Approximately 25% of patients have diabetes mellitus. Although the initial symptoms may be relatively mild, the disorder often progresses rapidly and is associated with a high risk of gallbladder perforation. The diagnosis can be made with plain abdominal radiographs, ultrasonographic studies, or CT. CT is the most sensitive method for detecting small amounts of gas in the gallbladder wall. Treatment includes intravenous antibiotics that cover anaerobic organisms, followed by early open or laparoscopic cholecystectomy. Another option is percutaneous drainage of the gallbladder, particularly in patients who are critically ill. Emphysematous cholecystitis has been reported in both gallstone cholecystitis and acalculous cholecystitis and has been associated with a mortality rate of approximately 15%. This is substantially higher than the mortality rates of 3% to 4% for acute cholecystitis without gas-forming organisms.

Porcelain gallbladder is seen more frequently in women, primarily in the sixth decade. It can be identified on plain abdominal radiographs or CT and is an uncommon finding in chronic cholecystitis. Porcelain gallbladder is characterized by extensive calcification manifested as a brittle consistency of the wall and is seen in less than 1% of cholecystectomy specimens, with stones identified in 95% of pathology specimens. It is an important diagnosis because of its association with gallbladder cancer. However, making the diagnosis may be difficult because of rim calcifications noted in the right upper quadrant that may be due to gallstones or liver, renal, adrenal, or pancreatic cysts. The incidence of gallbladder cancer in cases of porcelain gallbladder ranges from 0% to 20%. Prophylactic cholecystectomy is the treatment of choice for porcelain gallbladder.

Clinical Investigations

Liver Biochemical Testing

Uncomplicated biliary colic usually is not accompanied by changes in hematologic and biochemical test results. However, the initial evaluation of suspected stone disease should include serum liver biochemical testing (eg, alanine aminotransferase, aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) and transabdominal ultrasonography of the right upper quadrant. Liver biochemical tests may be most useful in excluding the presence of common bile duct stones. In a series of

more than 1,000 patients undergoing laparoscopic cholecystectomy, completely normal results on liver biochemical tests had a negative predictive value of more than 97%, whereas the positive predictive value of any abnormal liver biochemical test result was only 15%, according to the current guidelines of the American Society for Gastrointestinal Endoscopy.

Patients with cholangitis or pancreatitis associated with abnormal results on serum liver function tests are at increased risk for having bile duct stones. The conventional wisdom that the alkaline phosphatase level increases more than the AST level in obstructive jaundice holds true when jaundice is due to strictures, but in obstructive stone disease, the increase in AST may equal that in alkaline phosphatase or even exceed it during maximal jaundice and painful episodes. Occasionally, serum transaminase levels may be increased dramatically, mimicking acute viral hepatitis. With biliary stones, the increased levels tend to decrease rapidly over several days rather than weeks, as with acute viral hepatitis.

Biliary Imaging

Several improvements have been made in biliary imaging. Although ultrasonography is the primary initial modality for the evaluation of the biliary tree, the advent of and improvements in CT, magnetic resonance imaging, and endoscopic ultrasonographic (EUS) imaging techniques have resulted in superior detection and characterization of disease.

Plain Abdominal Radiography

Plain abdominal radiography can show radiopaque stones (about 25% of all stones) and pneumobilia due to a previous biliary sphincterotomy, a bilioenteric anastomosis or fistula, or an incompetent sphincter, as may occur with duodenal Crohn disease, duodenal diverticulum, or other periampullary disease.

Oral Cholecystography

Oral cholecystography involves standard radiographic imaging of the right upper quadrant after oral administration of an iodinated radiodense contrast agent. Thus, the agent needs to be ingested; absorbed, with liver uptake; excreted by the biliary system; and concentrated by the gallbladder. Most gallbladders opacify after a single oral dose, and 85% to 90% opacify after a second or double dose. Nonvisualization of the gallbladder after a reinforced 1- or 2-day study is 95% predictive of gallbladder disease. The use of oral cholecystography has diminished in clinical practice because it is less sensitive (65%-90%) than ultrasonography for cholelithiasis and it is not indicated when acute cholecystitis is suspected. Oral cholecystography may be useful when ultrasonography does not image the gallbladder and EUS is not available.

HIDA Scanning

HIDA scanning, also known as *cholescintigraphy*, may be used to diagnose acute cholecystitis or to confirm intra-abdominal bile leakage. This method involves noninvasive scanning of gamma emissions after the intravenous administration, liver uptake, and biliary excretion of technetium iminodiacetic acid derivatives. The inability to visualize the gallbladder despite excretion into the common bile duct at 4 hours after the injection is indicative of cystic duct obstruction. Nonvisualization of the gallbladder is 97% sensitive and 96% specific for acute calculous cholecystitis. False-negative results occur with acalculous cholecystitis, and false-positive results occur with chronic cholecystitis and chronic liver disease and during total parenteral nutrition or fasting states.

Transabdominal Ultrasonography

Ultrasonography has greater sensitivity for detecting dilatation of the common bile duct than for detecting choledocholithiasis. It is most sensitive (90%-98%) for the detection of cholelithiasis (>2 mm) identified as mobile, intraluminal, echogenic, shadowing particles. Obesity and bowel gas make interpretation challenging, but ultrasonography is relatively inexpensive and noninvasive compared with other imaging options. Cholecystitis is identified by gallbladder contraction or marked distention with surrounding fluid or wall thickening. Gallbladder thickening also may be due to portal hypertension, ascites, and hypoalbuminemia. The diameter of the common bile duct is normally 3 to 6 mm, and it may increase with advancing age. Biliary obstruction should be suspected when the diameter is more than 8 mm in a patient with a gallbladder in situ. Multiple small stones (<5 mm in diameter), compared with larger stones, increase the risk of common bile duct migration 4-fold. Transabdominal ultrasonographic examination of the gallbladder permits the visualization of particles in bile, usually those 2 to 3 mm or more in diameter.

Abdominal CT

CT is the best imaging method for the evaluation of possible complications of biliary stone disease if ultrasonography is suboptimal, as in patients with fever, right upper quadrant pain, and associated jaundice. Bowel gas and ribs do not interfere with CT. CT is superior to ultrasonography for obese patients, in whom imaging is improved by discrete fat planes. CT is not appropriate for the diagnosis of uncomplicated stone disease or evaluation of biliary colic because 50% of gallstones are radiolucent on CT.

Endoscopic Ultrasonography

Suspected Choledocholithiasis

The major advantage of EUS in suspected choledocholithiasis, as compared with transabdominal ultrasonography, is the ability to position the ultrasound transducer within the duodenal lumen, thereby allowing visualization of the adjacent biliary tree without interference from intestinal gas or abdominal fat. EUS is particularly important in correctly distinguishing acute biliary pancreatitis from other causes of pancreatitis.

Choledocholiths may be mobile, multiple, and of variable size (Figure 39.4). Occasionally, stones do not demonstrate acoustic shadowing and may be associated with a thickened bile duct wall. Bile duct sludge is seen as variably shaped and easily distorted echo-rich structures without acoustic shadowing.

In suspected choledocholithiasis, EUS has a sensitivity of more than 90% for the detection of common bile duct stones. The findings compare favorably with those of ERCP and are superior to those obtained with transabdominal ultrasonography, without the associated postprocedural ERCP risk of pancreatitis. For patients with a low or intermediate risk of bile duct stones, EUS is a cost-effective initial screening study. Comparative controlled trials of EUS and magnetic resonance cholangiopancreatography (MRCP) have demonstrated that the accuracy of EUS is comparable to or higher than that of MRCP for the detection of common bile duct stones.

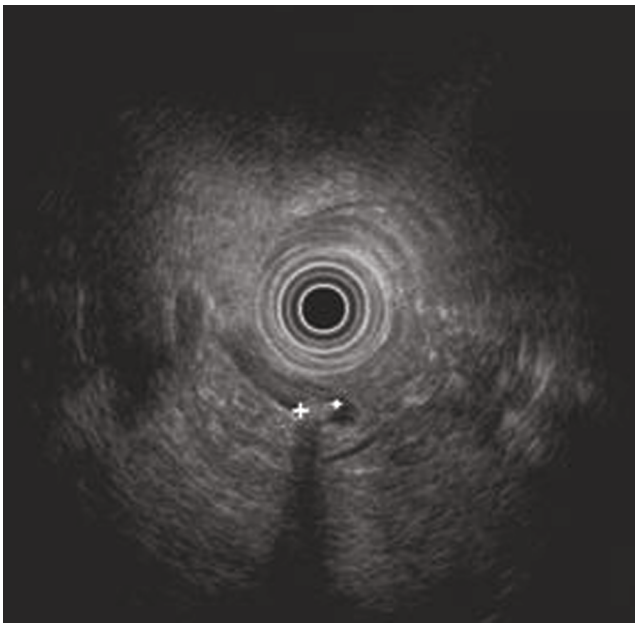

Figure 39.4. Endoscopic Ultrasonographic Image of Choledocholithiasis. Echo-rich areas with typical postacoustic shadowing are seen within the common bile duct.

A recent systematic review has suggested that EUS should be reserved for the evaluation of patients with an intermediate suspicion of common bile duct stones. Although EUS does not have the therapeutic capacity of ERCP for stone removal, algorithms have been developed that incorporate its use into clinical practice. Ultimately, the choice of modality should be based on clinical suspicion, availability of resources, experience, and cost.

Cholelithiasis

EUS can reliably identify cholelithiasis, particularly in obese patients with small stones. The appearance is that of a hyperechoic structure within the gallbladder, sometimes associated with an acoustic shadow. In patients with suspected gallbladder stone disease but with negative findings on conventional transabdominal ultrasonographic examinations, EUS has a sensitivity of 96% and a specificity of 86% compared with the corresponding cholecystectomy specimens or long-term clinical follow-up.

Microlithiasis

EUS has been shown to be as accurate as crystal analysis for the detection of microlithiasis (Figure 39.5). In approximately 20% of patients with acute pancreatitis, the cause is not established by history, physical examination, routine laboratory testing, or abdominal imaging. Recent studies suggest that microlithiasis may account for an unexplained attack of acute pancreatitis in as many as 75% of patients with a gallbladder in situ. Sphincter of Oddi dysfunction is most prevalent in patients with recurrent attacks who have previously undergone cholecystectomy. Therefore, EUS is an important diagnostic tool in evaluating patients who have unexplained biliary colic.

Polyps

With EUS, the normal gallbladder wall is seen as a 2- or 3-layer structure: The inner hypoechoic layer corresponds to the muscularis propria layer and the outer hyperechoic layer corresponds to an adipose layer. Cholesterol polyps are usually smaller than 10 mm in diameter and appear on ultrasonography as tiny echogenic spots or echogenic pedunculated masses without acoustic shadowing (Figure 39.6).

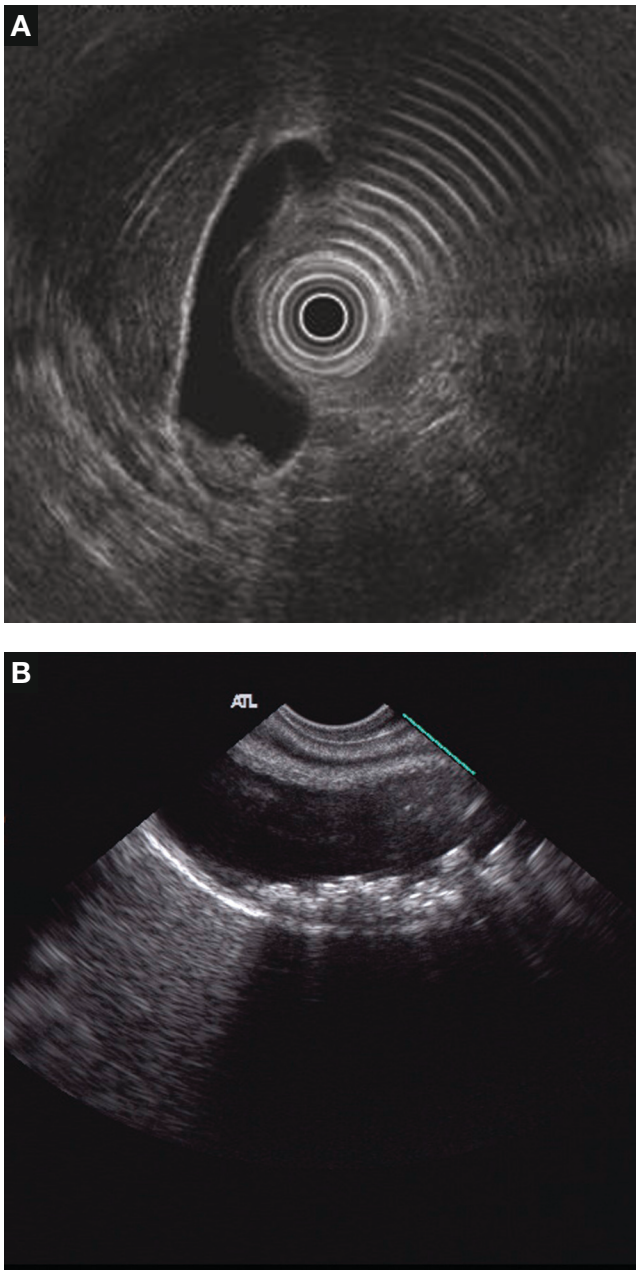

Figure 39.5. Microlithiasis on Endoscopic Ultrasonography. A, The crystals appear as floating hyperechoic foci that move when abdominal pressure is applied to the right upper quadrant and as layering material representing sludge. B, Note the presence of a shadowing stone with layering sludge.

Cholangiography

Cholangiography can be performed either invasively or noninvasively. The selection of MRCP, percutaneous transhepatic cholangiography, ERCP, or EUS-guided biliary access is based largely on the clinical setting and institutional expertise.

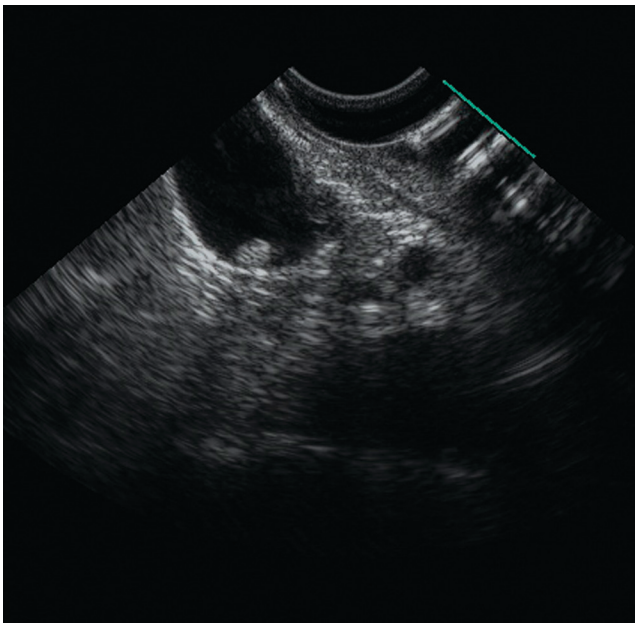

Figure 39.6. Cholesterol Polyps. Endoscopic ultrasonography shows an echogenic region without acoustic shadowing.

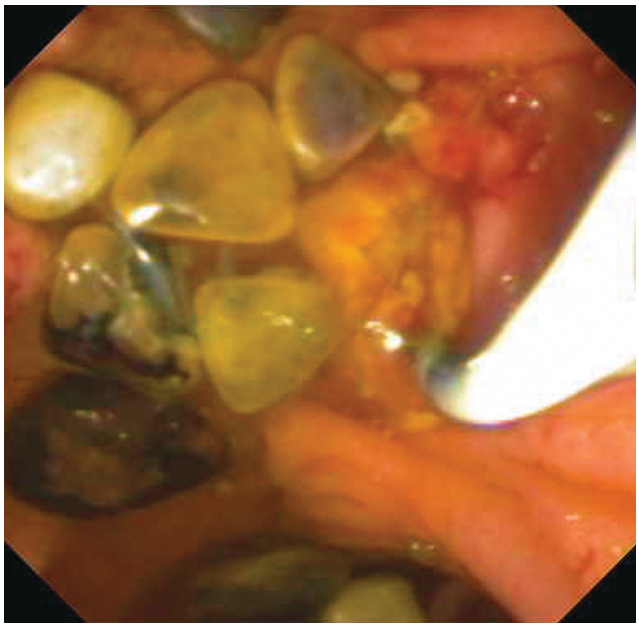

Figure 39.7. Cholesterol Stone Extraction. Multifaceted cholesterol stones are retrieved at endoscopic retrograde cholangiopancreatography.

Magnetic Resonance Cholangiopancreatography

MRCP or CT should be the first examination of choice because either is less invasive than EUS. Both methods have a similar ability for detecting stones, but MRCP may be preferable because of the possibility of a CT-associated allergic reaction. MRCP also is favored for frail patients who are not candidates for conscious sedation and for patients who have coagulopathy or who need concurrent staging or evaluation of the liver parenchyma or other organs, especially when there is little likelihood for therapeutic intervention. MRCP appears to be a valuable and safe technique for the evaluation of pregnant patients with acute pancreaticobiliary disease. Especially when ultrasonography shows biliary dilatation, MRCP can be used to determine the cause and prevent unnecessary ERCP by excluding biliary abnormality. When MRCP results are negative, EUS is recommended to check for small common bile duct stones.

Hemorrhagic cholecystitis is a form of acute cholecystitis often seen in the absence of gallstones. Hemorrhage is identified by the characteristic appearance of hemoglobin breakdown products within the wall or lumen of the gallbladder. A combination of MRCP and CT is useful for preoperative diagnosis of Mirizzi syndrome.

Percutaneous Transhepatic Cholangiography

Percutaneous transhepatic cholangiography may be favored for patients with a proximal obstruction (hilar or more proximal) or surgically distorted gastroduodenal anatomy (especially Roux limbs but also Whipple or Billroth II anatomy) and after failure of previous ERCP. It is almost uniformly successful in patients with dilated ducts and in 75% to 95% of those with nondilated ducts. The overall risk, including death, sepsis, bile leaks, and intraperitoneal bleeding, is 3% to 8%.

Endoscopic Retrograde Cholangiopancreatography

ERCP is favored for patients with ascites or coagulation defects, suspected periampullary or pancreatic neoplasia, nondilated ducts, anticipated need for therapeutic maneuvers (stone removal and stenting), or hypersensitivity to contrast agents and if percutaneous routes have failed. Purely diagnostic use is diminishing rapidly because, for most patients, EUS and MRCP serve this purpose more safely. ERCP is successful in more than 95% of diagnostic applications, in 90% to 95% of sphincterotomies and complete stone extraction, and in 90% of procedures for stenting of malignant obstruction (Figure 39.7). Nonemergent ERCP in patient 80 years or older is reported to be safe and cost-effective, with no significantly greater complication or mortality rate. Intraductal shock wave lithotripsy offers a therapeutic option that may be effective despite the difficulties of a large, impacted stone that cannot be captured by a basket or a stricture that prohibits delivery of a stone beyond it. The overall risk of the procedure in patients with suspected gallstones is 2% to 7% for diagnostic

Box 39.3. Gallstone Treatments

Indications for cholecystectomy (open or laparoscopic)

- Symptomatic cholelithiasis (with or without complications)
- Asymptomatic cholelithiasis in patients who are at increased risk for gallbladder carcinoma or gallstone complications
- Acalculous cholecystitis
- Gallbladder polyps >0.5 cm in diameter
- Porcelain gallbladder

Nonsurgical treatment of gallbladder stones

- Oral bile acid dissolution therapy with ursodiol for cholesterol stones
- Extracorporeal shock wave lithotripsy

Table 39.2. Mimics of Biliary Colic

Condition	*Comments*
Intravenous ceftriaxone therapy	May lead to formation of crystalline biliary precipitates of drug Ceftriaxone crystals can induce all potential complications of small bile duct stones, including biliary colic and pancreatitis
Erythromycin hepatotoxicity	Manifests as syndrome of pain, fever, and cholestatic hepatitis, mimicking acute cholecystitis Eliciting antibiotic history during evaluation of symptoms is important Consistent history and associated eosinophilia may help identify syndrome
Leptospirosis	Weil syndrome (characterized by fever, jaundice, azotemia, and right upper quadrant pain) mimics acute bacterial cholangitis Clues to diagnosis include history of exposure risk, myalgias, ocular pain, photophobia, azotemia, and abnormal urinalysis findings

procedures and 7% to 10% for therapy. Risks include death, pancreatitis, infection, sedation or cardiovascular events, hemorrhage, and perforation.

For patients who have gallstone pancreatitis and concomitant cholangitis, ERCP should be performed within 24 hours. If a persistent common bile duct stone is highly likely (visible common bile duct stone on noninvasive imaging, persistently dilated common bile duct, and jaundice), patients should undergo ERCP within 72 hours. Although data are lacking to support the practice of endoscopic sphincterotomy in the absence of choledocholithiasis at the time of the procedure, the practice is a reasonable therapeutic option. ERCP and sphincterotomy alone may provide adequate long-term therapy for patients who are not candidates for surgery. Cholecystectomy should be performed during the same hospital admission if possible and no later than 2 to 4 weeks after discharge for patients with a gallbladder in situ.

Gallstone treatments are listed in Box 39.3, and mimics of biliary colic are listed in Table 39.2.

Suggested Reading

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Questions and Answers

Questions

Abbreviations used:

AIP, autoimmune pancreatitis
ALT, alanine aminotransferase
APACHE, Acute Physiology and Chronic Health Evaluation
AST, aspartate aminotransferase
BMI, body mass index
CT, computed tomography
ERCP, endoscopic retrograde cholangiopancreatography
EUS, endoscopic ultrasonography
HAPS, harmless acute pancreatitis score
ICU, intensive care unit
MRI, magnetic resonance imaging
PCA, patient controlled analgesia
SUN, serum urea nitrogen
ULRR, upper limit of the reference range
WBC, white blood cell

Multiple Choice (choose the best answer)

VII.1. **A 32-year-old woman, gravida III and para III, who is otherwise healthy presents to the emergency department with a 12-hour history of severe, steady epigastric pain radiating to the back and associated tenderness on examination. Laboratory test results are shown below:**

Component	Result
Amylase, U/L	105 (ULRR <110)
Lipase, U/L	280 (ULRR <60)
Triglycerides, mg/dL	440
AST, U/L	90
ALT, U/L	120
Calcium, mg/dL	8.4
Hemoglobin, g/dL	14
Hematocrit, %	42
Platelet count, $\times 10^3/\mu L$	350

Which of the following is true about her presentation?

a. The normal amylase level largely excludes acute pancreatitis
b. The normal amylase is spurious and artificially suppressed by the hypertriglyceridemia, which is the likely cause of pancreatitis
c. The laboratory test results are nonspecific, and CT is required to make a diagnosis of pancreatitis
d. The normal amylase and elevated lipase levels reflect the earlier return of total amylase values to the reference range, which accommodates amylase from multiple sources
e. Macroamylasemia is likely because of the lack of correlation between the amylase and lipase values

VII.2. **The patient in the previous question has elevated liver enzyme levels and a history of hepatitis A several years ago. Her liver test results were normal on a general blood chemistry panel during an annual physical examination in the past year. Abdominal ultrasonography now shows only modest sludge in the gallbladder and bowel gas obscuring the pancreas. Which of the following is true about her presentation?**

a. The elevated transaminases most likely represent steatohepatitis related to her hypertriglyceridemia
b. The transaminase elevations, if new, reflect acute bile duct obstruction and are highly specific for a biliary cause of pancreatitis
c. The absence of stones in the gallbladder makes a biliary source of pancreatitis unlikely
d. The transaminase elevations indicate that ERCP should be undertaken early in the patient's hospital stay
e. Persistent transaminase elevations at 12 hours should prompt more aggressive hydration and use of antibiotics at the outset of care

VII.3. **A 59-year-old male attorney is admitted through the emergency department with severe abdominal pain, nausea, and vomiting. On examination, he is obese (body weight 100 kg,**

height 175 cm, BMI 32.5) and has exquisite epigastric tenderness, tachycardia, and tachypnea. The amylase and lipase values are each greater than 1,000 U/L. Other laboratory test results are shown below:

Component	Result
Hemoglobin, g/dL	16
Hematocrit, %	48
WBC count, /μL	11,500
Platelet count, $\times 10^3$/μL	450
Creatinine, mg/dL	1.0
SUN, mg/dL	33
AST, U/L	48
ALT, U/L	55
Triglycerides	Normal
Calcium	Normal

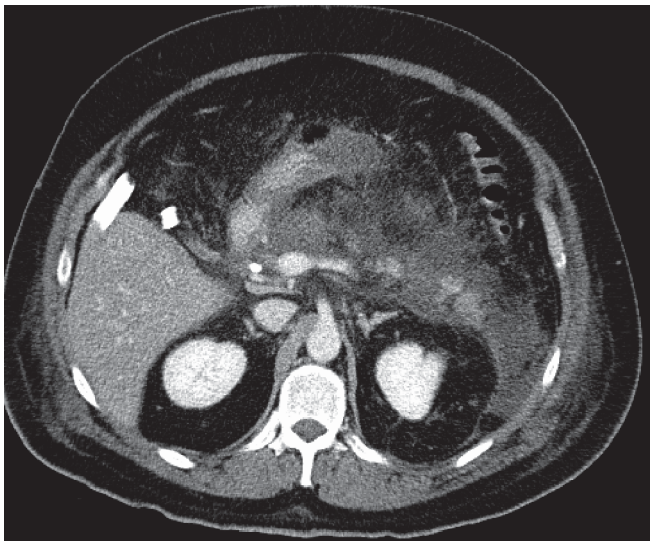
Which of the following are appropriate steps, given the anticipated severity of his pancreatitis?

a. The patient's younger age, relatively modest obesity, and normal creatinine level suggest that his course will be mild, so efforts should focus on identifying the underlying cause
b. The HAPS predicts a mild course for this patient, particularly given the normal creatinine level
c. Risk factors for a severe episode include the patient's age, weight, relative hemoconcentration, and evidence of respiratory compromise, so initial management should focus on aggressive fluid administration and close monitoring
d. The severity of his pancreatitis cannot be anticipated for 48 hours, pending reassessment of the course of his liver enzymes, oxygenation, and CT assessment
e. CT should be done shortly after admission to facilitate estimation of the patient's prognosis, based on the presence or absence of necrosis

VII.4. The patient in the previous question is admitted to a general ward for initial management of his pancreatitis. Which of the following measures should be included in the first steps?

a. Analgesia (fentanyl 50 mcg hourly) and hydration (normal saline 175 mL hourly) should be continued aggressively over the first 24 hours.
b. ERCP should be considered early because the prognostic features predict a severe course and delayed intervention will be more difficult
c. The patient should receive nothing by mouth for now, and the route and rate of nutritional supplementation should be further considered after 3 to 4 days, when the duration of his course becomes clearer
d. Parenteral antibiotics are not indicated in acute pancreatitis, but oral selective bowel decontamination should be considered if the course will be prolonged
e. Close monitoring should be initiated on admission, with frequent serial assessment of fluid intake and output, vital signs, respiratory status, and at least daily testing for SUN, creatinine, calcium, and magnesium levels; hematocrit; hemoglobin; and WBC count

VII.5. On day 3, the condition of the patient in the previous question deteriorates, and he has increasing respiratory difficulty, a low-grade fever, a pulse of 110 beats per minute, and a blood pressure of 92/60 mm Hg. Laboratory testing shows leukocytosis (WBC count 16,500/μL), amylase 900 U/L, hematocrit 50%, and creatinine 1.9 mg/dL. He undergoes CT. An image is shown. Which of the following are the most appropriate next steps?



a. ICU care for more intense monitoring during aggressive hydration; blood and urine cultures; CT-guided aspiration of the pancreas; semiempirical antibiotic therapy; and potential supportive management in the event of progression to respiratory or renal failure
b. Interventional radiology for percutaneous decompression of pancreatic and peripancreatic necrosis and infection
c. Surgical ICU service for close monitoring and the potential need for open necrosectomy in the coming days
d. ICU care for more intense monitoring before and after endoscopic necrosectomy
e. ICU care to enable administration of greater fluid volumes through a change from enteral to parenteral nutrition and to facilitate daily CT scans to assess the evolution and possible infection of his fluid collections

VII.6. A 15-year-old male patient presents with abdominal pain, obstructive jaundice, and a diffusely enlarged pancreas on MRI and EUS. The serum level of IgG4 is normal, and he has no evidence of involvement of any other organ. Which of the following features is likely to be seen on pancreatic histology?

a. Obliterative arteritis
b. Acute inflammation without fibrosis
c. Neutrophilic infiltrate in the pancreatic duct epithelium
d. Lymphocytic epithelial lesion

VII.7. A 20-year-old woman has had bouts of pancreatitis twice a year for the past 5 years. She has a strong family history of pancreatitis; her older brother, father, and paternal grandfather also have had pancreatitis. She consumes 2 or 3 glasses of beer on the weekends but does not smoke. Her CT scan shows scattered pancreatic calcification. The early age at onset suggests a genetic cause of pancreatitis. Mutation in which of these genes would be the most likely cause of her chronic pancreatitis?

a. *PRSS1* (cationic trypsinogen)
b. *CFTR*
c. *SPINK1*
d. Chymotrypsinogen C (*CTRC*)
e. Calcium-sensing receptor (*CASR*)

VII.8. A 45-year-old man received a diagnosis of recurrent pancreatitis 6 months ago when he experienced multiple bouts of severe abdominal pain with increased amylase levels (>3 times the ULRR). He continues to have chronic low-grade abdominal pain exacerbated by meals. He smokes 1 pack of cigarettes daily and drinks 2 or 3 glasses of wine on weekends. No pancreatic abnormalities are noted on his CT. EUS shows lobularity and stranding of the parenchyma, ectatic

side branches of the pancreatic duct, and small shadowing calculi in the main pancreatic duct. He wonders whether he has chronic pancreatitis. Which of the following features definitively confirms diagnosis of chronic pancreatitis in this patient?

a. Frequent bouts of pancreatitis
b. Persistent, mild increases in serum amylase (<2 times the ULRR)
c. Chronic abdominal pain following acute pancreatitis 6 months earlier
d. Intraductal calculi on EUS
e. Increased serum IgG4 levels

VII.9. A 52-year-old man received a diagnosis of AIP 12 months ago. Since then he has had a relapse. Both his initial presentation and his relapse episode were treated with steroids. Now he presents with foul-smelling diarrhea and a 13.6-kg weight loss despite a voracious appetite. Which of the following statements is true?

a. Steatorrhea requires loss of at least 30% of pancreatic function
b. Oral pancreatic enzyme supplements should be taken half an hour before meals
c. Steatorrhea is not a complication of AIP
d. Approximately 3,000 to 4,500 US Pharmacopeia units of amylase should be given with every meal
e. Correction of steatorrhea with oral enzyme supplements usually is associated with correction of carbohydrate and protein malabsorption

VII.10. A 40-year-old alcoholic man received a diagnosis of chronic calcific pancreatitis 5 years ago. He continues to have bouts of pancreatitis that require hospitalization for 7 to 10 days. Between episodes, he has postprandial discomfort that is often disabling for a few hours. CT shows a diffusely dilated pancreatic duct (8 mm in size) with numerous calculi. No dominant stricture or occluding stone is seen. Which of the following statements is true?

a. The patient should be managed conservatively since he will soon develop a painless "burnout" of chronic pancreatitis
b. Longitudinal pancreaticojejunostomy will provide lasting relief from pain and pancreatitis
c. Shockwave lithotripsy with repeated ERCP to clear the duct of stones is the best approach to management
d. The preferred surgical option is a pancreaticoduodenectomy
e. All the above procedures will dramatically improve exocrine and endocrine pancreatic function

VII.11. A 65-year-old woman with an unremarkable medical history complains of vague, infrequent right upper quadrant discomfort. Transabdominal ultrasonography shows a 19-mm, fixed, hyperechoic lesion protruding into the lumen of the gallbladder without an acoustic shadow. Which of the following should you recommend at this time?

a. Annual surveillance
b. No surveillance
c. Open cholecystectomy
d. Cholecystotomy
e. Laparoscopic cholecystectomy

VII.12. Four weeks previously, a 24-year-old man had his first episode of uncomplicated acute pancreatitis due to an alcohol binge and required a 3-day hospital stay. He now presents for your opinion regarding asymptomatic gallbladder microlithiasis detected with EUS and normal liver biochemistry results. Which of the following should you recommend?

a. Laparoscopic cholecystectomy
b. ERCP
c. No management of microlithiasis at this time
d. Oral cholecystography with cholecystokinin
e. Transabdominal ultrasonography

VII.13. A 32-year-old diabetic woman (22 weeks pregnant) has had 4 episodes of biliary colic over the preceding month and now presents with sustained right upper quadrant abdominal pain, fever, and leukocytosis. Liver biochemical test results are unremarkable. Which of the following should you recommend at this time?

a. ERCP
b. Laparoscopic cholecystectomy
c. Transabdominal ultrasonography in 1 week
d. Abdominal CT scan in 48 hours
e. EUS in 4 weeks

VII.14. An 18-year-old patient who has cystic fibrosis and had recent total parenteral nutrition has frequent epigastric discomfort. Findings from upper endoscopy are unremarkable. Transabdominal ultrasonography shows multiple, mobile 4- to 5-mm filling defects in the common bile duct. Which of the following is most likely to be present?

a. *Ascaris lumbricoides*
b. Black pigment common bile duct stone
c. *Opisthorchis sinensis*
d. Cholesterol common bile duct stone
e. Brown pigment common bile duct stone

VII.15. Which of the following is *not* involved in cholesterol crystal formation?

a. Bile stasis
b. Cholesterol supersaturation
c. Accelerated nucleation
d. Genetic factors
e. Gallbladder hypermotility

VII.16. Which of the following is *not* a congenital anomaly of the gallbladder?

a. Phrygian cap
b. Hourglass gallbladder
c. Gallbladder agenesis
d. Macro-gallbladder
e. Wandering gallbladder

Answers

VII.1. Answer d.
In acute pancreatitis, elevated serum amylase values decrease to the reference range much faster than serum lipase values, because total serum amylase includes amylase contributed by multiple sources. Lipase is more specific to the pancreas; hence, lipase levels reflect pancreatic pathology with greater sensitivity. The other answer choices are incorrect for the following reasons: The elevated lipase level makes the diagnosis in the appropriate clinical setting. Spuriously low amylase levels are seen with much higher triglyceride levels, and only levels above 1,000 U/L are reliably incriminated as the cause of acute pancreatitis. The lipase elevation is specific for pancreatitis, and CT is not required for diagnosis. CT may be normal or show inflammatory changes in mild pancreatitis. Macroamylasemia causes spurious elevations in amylase levels without underlying pancreatitis.

VII.2. Answer b.
Acute transaminase elevations (ALT in particular) in a patient with pain, are strongly indicative of a biliary cause of acute pancreatitis. Three-fold elevations have a positive predictive value

of 90%, but they are only 50% sensitive for a biliary source. The other answer choices are incorrect for the following reasons: A patient with steatohepatitis would be expected to have long-term enzyme abnormalities without pain. Biliary sludge is a marker for stone-forming physiology and can cause biliary pancreatitis on occasion. Short-term transaminase elevations can develop even when stones pass, and they do not reflect persistence of stones or presence of associated cholangitis. Early ERCP is indicated only for severe acute pancreatitis with associated biliary obstruction or infection. Transaminase elevations do not correlate with severity of pancreatitis, presence of necrosis, or adequacy of hydration.

VII.3. Answer c.
Age older than 55 years, obesity (BMI >30), organ failure at admission (especially renal or respiratory), and pleural effusions have been identified as risk factors for a severe course. Hemoconcentration, reflected in an elevated hematocrit or SUN, is also predictive of severe disease. The other answer choices are incorrect for the following reasons: His age and obesity are risks for severe disease. The creatinine is encouraging, but the SUN may reflect hemoconcentration. The HAPS requires the presence of all 3 defining features to predict a benign or mild course, including absence of rebound, normal hematocrit, and normal creatinine, which together have a 98% positive predictive value for a mild course. Hemoconcentration, the HAPS score, elevated C-reactive protein, and the clinical features noted in answer choice *c* are all single-point-in-time features that can help with assessing prognosis for an episode of acute pancreatitis. The Ranson and APACHE II scores require follow-up testing over 24 to 48 hours for complete assessment. The Balthazar score can help estimate severity and prognosis for patients with acute pancreatitis, but CT scans done in the first 48 hours often underestimate the extent and severity of nonperfusion and subsequent necrosis. If not needed for the actual diagnosis of pancreatitis, or assessment of other potential insults, CT characterization should be delayed for 48 to 72 hours.

VII.4. Answer e.
Key steps in early management of acute pancreatitis are analgesia by PCA pump (if coherent), aggressive hydration (normal saline or lactated Ringer solution 250-350 mL hourly), and close monitoring for hydration status and signs of organ failure. The other answer choices are incorrect for the following reasons: Analgesia should be given by PCA pump or intermittent boluses unless the patient is being monitored in an ICU or is being mechanically ventilated, and hydration should be given more aggressively than proposed in answer choice *a*. Early ERCP is not indicated for severe acute pancreatitis in the absence of biliary obstruction or infection. Nutrition should be instituted as early as the need can be anticipated—ideally, in the first 24 to 48 hours to maintain mucosal integrity of the gut. Enteral nutrition, generally by nasojejunal tube, is almost always the preferred route for supplementation. Antibiotics are not routinely required in acute pancreatitis, but many patients with severe disease and toxic features warrant antibiotic coverage once samples are obtained and until infection is excluded. Selective oral bowel decontamination has not been identified as useful in acute pancreatitis.

VII.5. Answer a.
The patient has signs of intravascular volume depletion, respiratory compromise, and possible infection. ICU care is warranted, and more aggressive supportive care is urgently needed, including fluid support, exclusion of infection, and possible mechanical ventilation in the coming hours or days. The other answer choices are incorrect for the following reasons: Percutaneous decompression is not indicated at this point, although it may be if the patient's condition continues to deteriorate and infected necrosis is identified by CT-guided aspiration. Open necrosectomy carries higher morbidity and mortality than less invasive options and it is no longer recommended for initial decompression or débridement in patients with sterile or infected necrosis. In the absence of infection, endoscopic necrosectomy is not indicated early during acute pancreatitis. Parenteral nutrition should be entertained only if the patient is intolerant of appropriate volumes by the enteral route. It is not a means of maximizing intravascular volume. Daily CT scans are not indicated for monitoring of pancreatitis.

VII.6. Answer c.
This patient's profile (young age, normal serum level of IgG4, and no other organ involvement) is most compatible with that of type 2 AIP, which has a unique histologic pattern that distinguishes it from other forms of chronic pancreatitis. The characteristic histologic feature of type 2 AIP is a granulocyte epithelial lesion with a neutrophilic infiltrate in the pancreatic duct epithelium leading to mucosal disruption and eventual obliteration of the lumen.

VII.7. Answer a.
Most cases of chronic pancreatitis are believed to be due to a combination of inherited susceptibility genes and environmental risk factors (eg, alcohol and smoking). The genetic factors include mutations in 1 or more of 6 genes associated with pancreatitis: cationic trypsinogen gene (*PRSS1*), anionic trypsinogen gene (*PRSS2*), serine protease inhibitor Kazal 1 gene (*SPINK1*), cystic fibrosis transmembrane conductance regulator gene (*CFTR*), chymotrypsinogen C gene (*CTRC*), and calcium-sensing receptor gene (*CASR*). Of these, only mutations in the cationic trypsinogen gene (R117H and N21I) are commonly associated with an autosomal dominant pattern of inheritance of pancreatitis. For this patient, the history of early onset of pancreatitis and the strong family history of pancreatitis are highly suggestive of hereditary chronic pancreatitis. Mutations in *SPINK1* and *CFTR* genes are associated with idiopathic pancreatitis. Although heavy smoking and alcohol use, alone or in combination, can predispose to chronic pancreatitis, they would not explain this patient's striking family history of pancreatitis.

VII.8. Answer d.
Without a definitive histologic study, the diagnosis of chronic pancreatitis is made by considering the results of clinical, imaging, biochemical, and pancreatic function studies. Recurrent acute pancreatitis attacks may occur without underlying chronic pancreatitis. Persistent, mild increases in serum amylase levels indicate the possibility of macroamylasemia, a benign asymptomatic condition. Chronic abdominal pain following an episode of acute pancreatitis may be due to a complication of pancreatitis but is rarely due to chronic pancreatitis. EUS findings can be abnormal in alcoholic persons without pancreatitis. An EUS study showing intraductal stones is highly suggestive of chronic pancreatitis, whereas normal EUS findings virtually exclude chronic pancreatitis. This patient's clinical picture is not suggestive of type 1 AIP. Therefore, an elevated serum level of IgG4 is likely to be a false-positive result.

VII.9. Answer e.
More than 90% of pancreatic function has to be lost to cause steatorrhea. Oral pancreatic enzyme supplements should be taken throughout the meal. Enzymes taken before or after a meal are not as effective as enzymes taken during the meal. AIP often results in

pancreatic atrophy and steatorrhea. Approximately 30,000 to 45,000 US Pharmacopeia units of lipase should be given with every meal. Correction of steatorrhea with oral enzyme supplements is associated with correction of carbohydrate and protein malabsorption.

VII.10. Answer c.
It is debated whether chronic pancreatitis eventually "burns out" and becomes painless. However, for this patient, waiting without intervention is not an option because he is symptomatic. Randomized controlled trials suggest that for patients who have chronic calcific pancreatitis with a dilated duct, the preferred intervention is a drainage procedure such as lateral pancreaticojejunostomy. However, none of the interventions will improve pancreatic exocrine or endocrine function.

VII.11. Answer c.
The prevalence of gallbladder adenomas or polyps is reported as 4% to 7%. A gallbladder polyp larger than 18 mm has a high likelihood of being an advanced cancer and should be removed by open cholecystectomy with possible liver and lymph node dissection.

VII.12. Answer c.
Microlithiasis may be an etiologic factor or a secondary event following an episode of acute pancreatitis. In this case, no further evaluation or intervention is required unless a second episode develops.

VII.13. Answer b.
Pregnant women with symptomatic gallbladder disease who undergo operative intervention rather than conservative care have superior outcomes. Patients treated conservatively are more likely to undergo cesarean delivery.

VII.14. Answer b.
Ascaris lumbricoides and *Opisthorchis sinensis* are seen in patients with recurrent pyogenic cholangitis. In addition to cystic fibrosis and total parenteral nutrition, black pigment stones may be seen in patients with chronic hemolytic states, mechanical heart valves, cirrhosis, and Gilbert syndrome.

VII.15. Answer e.
Gallbladder *hypomotility* or impaired gallbladder emptying may prolong bile presence in the gallbladder, permitting extra time for nucleation of cholesterol crystals from supersaturated bile.

VII.16. Answer d.
A micro-gallbladder, rather than a macro-gallbladder, is less than 2 to 3 cm long and 0.5 to 1.5 cm wide. It is associated with cystic fibrosis and idiopathic neonatal hepatitis. A phrygian cap is an inversion of the gallbladder fundus into the body, to which it may become adherent. This may be an anatomical congenital variant or an acquired abnormality. An hourglass gallbladder is divided by a central constriction and is a variant of a transverse septate gallbladder. Gallbladder agenesis is rare, is of no clinical significance, and is associated with choledocholithiasis and duodenal atresia. A wandering gallbladder has either a long mesentery or no firm attachment to the liver and is at risk for torsion.

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