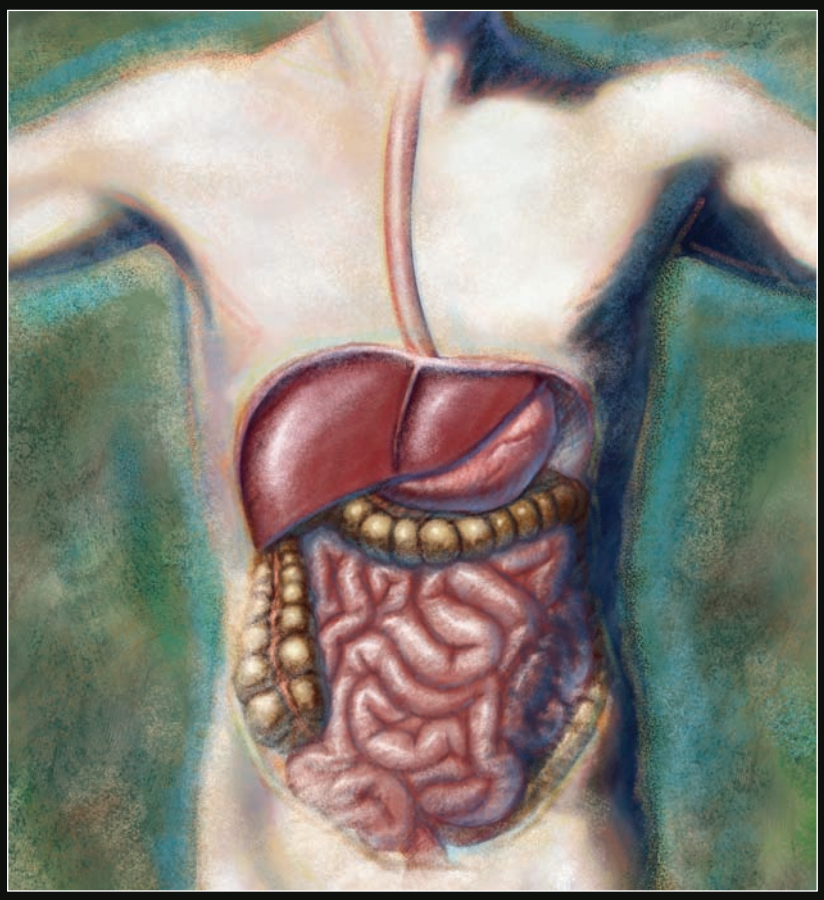
Mayo Clinic Gastroenterology and Hepatology Board Review

Third Edition



Editor
Stephen C. Hauser, MD

Co-Editors
Darrell S. Pardi, MD
John J. Poterucha, MD

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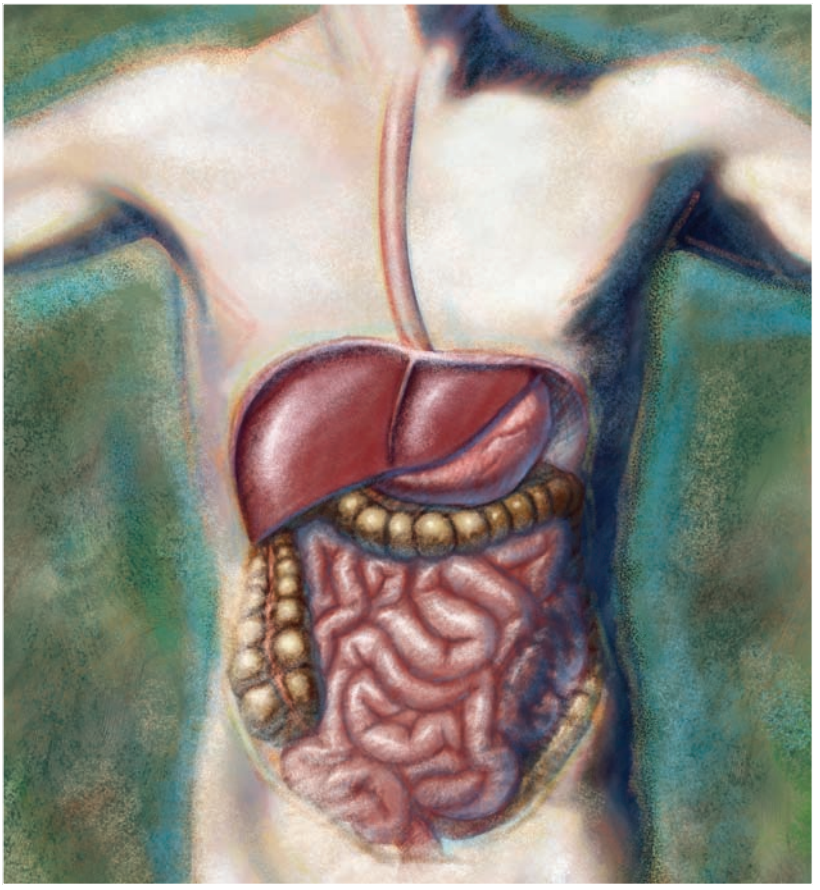

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DEDICATION

To the many persons who have taught, encouraged, and inspired us.

PREFACE

Gastroenterology and hepatology encompass a large assortment of organs with diverse structure and function that potentially are afflicted by a multiplicity of disease processes. We have designed the revised edition of the Mayo Clinic Gastroenterology and Hepatology Board Review book and course to assist physicians-in-training who are preparing for the gastroenterology board examination and the growing number of gastroenterologists who are awaiting recertification. The book is not intended to replace the more encyclopedic textbooks of gastroenterology, hepatology, pathology, endoscopy, nutrition, and radiology now available. Nor is it intended to serve as an "update" to physicians who are looking for the newest advances in the science and art of gastroenterology and hepatology. Instead, this book is intended to provide 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 multiple short board-examination–type, single best-answer questions with annotated answers are featured. As such, this text also is intended to be used by medical students and residents for their clerkships during rotations in internal medicine and gastroenterology and by gastroenterology fellows in training. Physicians in practice should find this book to be a practical review to consolidate their knowledge in gastroenterology and hepatology.

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 are used to illustrate the text. Each subspecialty section concludes with a chapter containing multiple board examination-type, single best-answer multiple-choice questions with annotated answers. Materials in the questions and answers are not included in the index. The faculty responsible for the book at the time of its production are all Mayo Clinic gastroenterologists and hepatologists who spend most of their time caring for patients, but who also 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, providing broad expertise.

We thank the staffs of the Section of Scientific Publications, Media Support Services, and the Mayo School of Continuing Medical Education at Mayo Clinic for their help in producing this book. The support of the publisher, Mayo Clinic Scientific Press and Informa Healthcare USA, also is greatly appreciated. We also want to give special thanks to our secretaries and to Dr. Greg Gores for his ongoing enthusiasm and support for our faculty and teaching mission.

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SECTION I

Esophagus

Chapter 1

Gastroesophageal Reflux Disease

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 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 (Table 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 (Fig. 1). The relative contribution of these varies from patient to patient.

Table 1. Etiologic Factors of Gastroesophageal Reflux Disease

Motility disorders
Transient lower esophageal relaxations*
Weak lower esophageal sphincter*
Weak esophageal peristalsis
Scleroderma and CREST
Delayed gastric emptying
Damaging factors
Increased gastric acid production
Bile and pancreatic juice
Resistance factors
Reduced saliva and HCO_3 production
Diminished mucosal blood flow
Growth factors, protective mucus
Others
Hiatal hernia*
Obstructive sleep apnea

CREST, calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia.
**Major/common factors.*

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

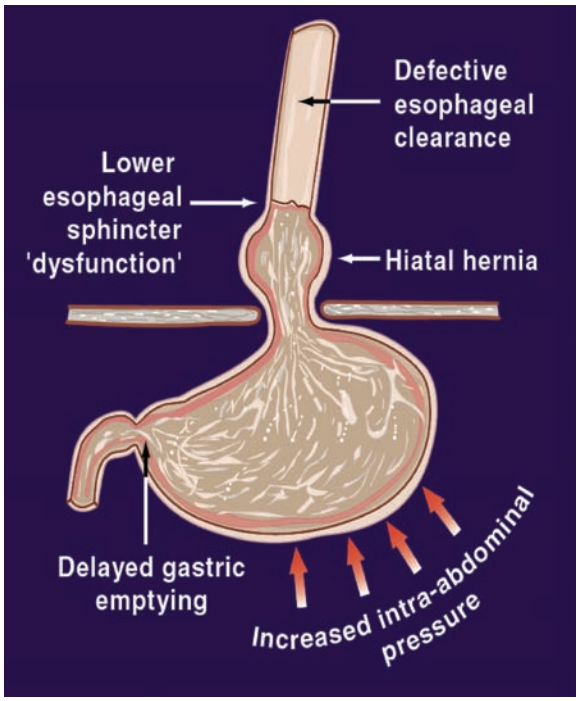

Fig. 1. Causes of increased exposure of the esophagus to gastric refluxate. (From AstraZeneca Pharmaceuticals LP [Internet]. Wilmington (DE). Available from: http://www.astrazeneca.com. Used with permission.)

FACTORS CONTRIBUTING TO GASTROESOPHAGEAL REFLUX DISEASE

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 is 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 latter relaxation has been termed *transient lower esophageal sphincter relaxation* (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 lowering the threshold for TLESRs 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's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome or scleroderma. Many drugs and Sjögren's 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 (Fig. 2 and 3).

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

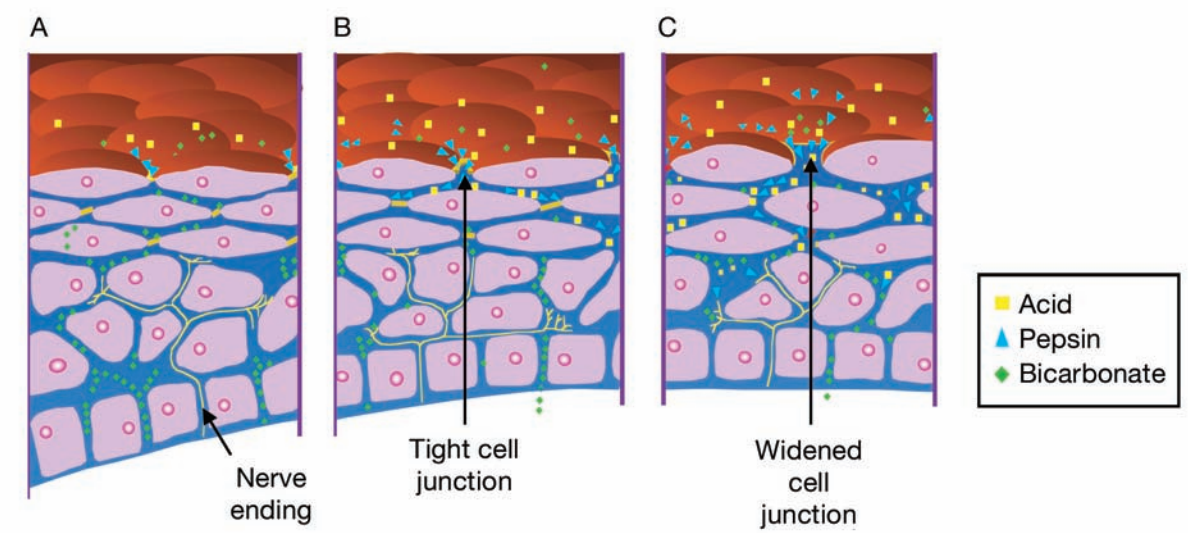

Fig. 2. Mechanism of action of refluxate in gastroesophageal reflux disease. The sequence of events hypothesized to lead to symptoms and tissue damage in gastroesophageal reflux disease is as follows: *A* and *B*, Acid-peptic attack weakens cell junctions and, *C*, widens the cell gaps, thus allowing acid penetration. Exposure to gastric acid and pepsin can cause microscopic damage to the esophageal mucosa, which may not be visible endoscopically but still result in heartburn. (From AstraZeneca Pharmaceuticals LP [Internet]. Wilmington (DE). Available from: http://www.astrazeneca.com. Used with permission.)

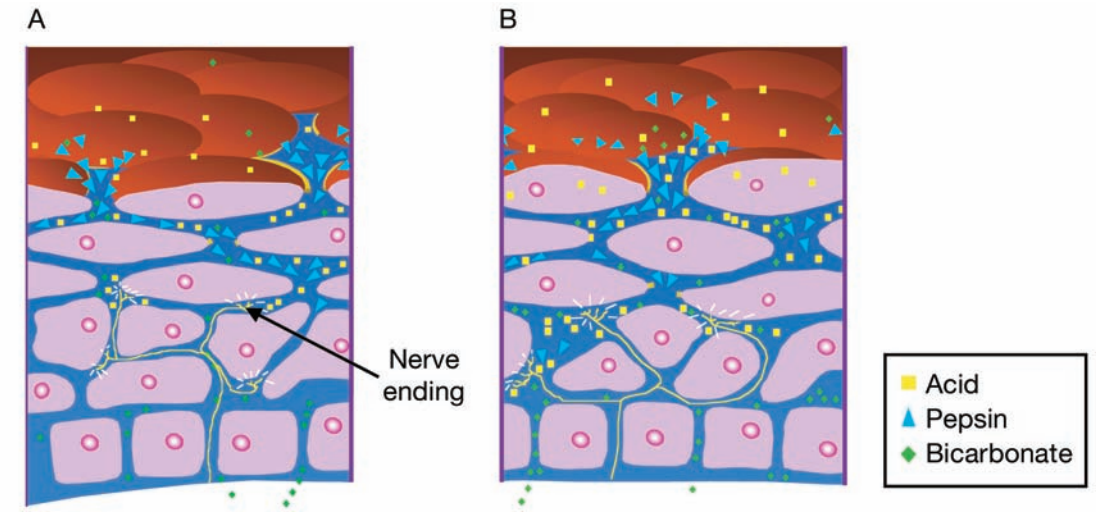

Fig. 3. Mechanism of action of refluxate in gastroesophageal reflux disease. *A*, Penetration of acid and pepsin into the mucosa allows contact of acid with epithelial nerve endings (which may result in heartburn). *B*, Additional influx of acid and pepsin into the mucosa triggers a cascade of events ultimately leading to cell rupture and mucosal inflammation. (From AstraZeneca Pharmaceuticals LP [Internet]. Wilmington (DE). Available from: http://www.astrazeneca.com. Used with permission.)

abdominal straining. The cardia is often submerged under liquid gastric contents in the recumbent, especially in the right lateral decubitus, position. It has been suggested recently 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.

Helicobacter pylori and Gastroesophageal Reflux Disease

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, which included *H. pylori* eradication, for the new development of GERD symptoms. The evidence is conflicting 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 (Fig. 4). Other explanations for the apparent occurrence of GERD after the eradication of *H. pylori* may include unrecognized GERD injury or symptoms present before eradication, rebound acid secretion after cessation of potent acid suppression, or other unrelated factors.

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's 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 (Fig. 5).

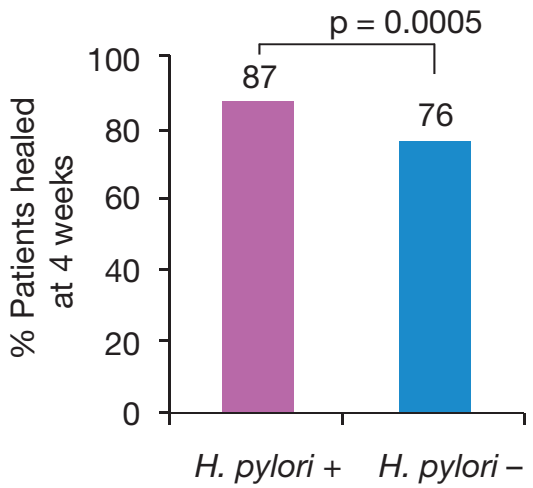

Fig. 4. The efficacy of proton pump inhibitor therapy may be greater in patients with gastroesophageal reflux disease who are positive for *Helicobactor pylori* (*H. pylori* +) than in those negative for *H. pylori* (*H. pylori* –).

Mechanism of 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 (Fig. 6).

EPIDEMIOLOGY OF GASTROESOPHAGEAL REFLUX DISEASE

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

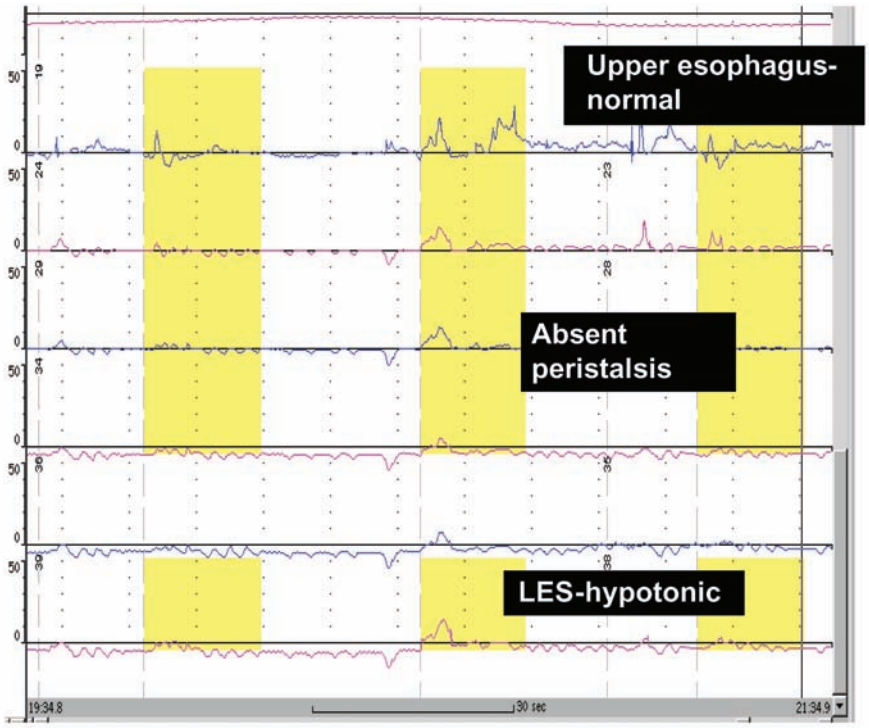

Fig. 5. Esophageal manometric tracing illustrating complete absence of peristalsis or absence of lower esophageal sphincter (LES) pressure consistent with involvement of the esophagus by scleroderma.

suggestive of GERD are common: 40% of the adult population in the United States report heartburn monthly and 18% report it weekly (Fig. 7). GERD becomes more common with increasing age (Fig. 8). 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 fewer 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's 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.

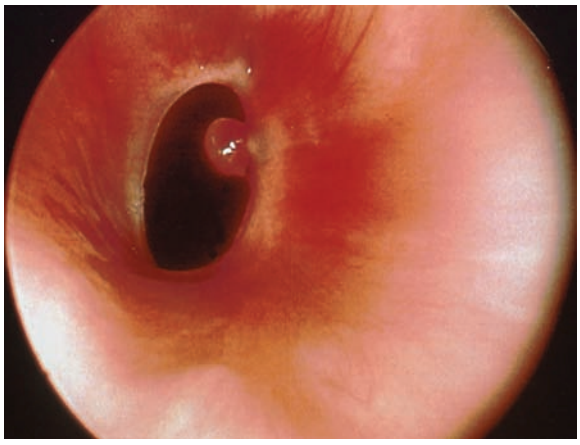

Fig. 6. Laryngeal stenosis. (Courtesy of Dr. Dana Thompson, Otorhinolaryngology/Pediatric Otolaryngology, Mayo Clinic.)

For patients with GERD, the quality of life may be impaired even more than for those with congestive heart failure or angina pectoris (Fig. 9). Treatment of GERD has important health economic

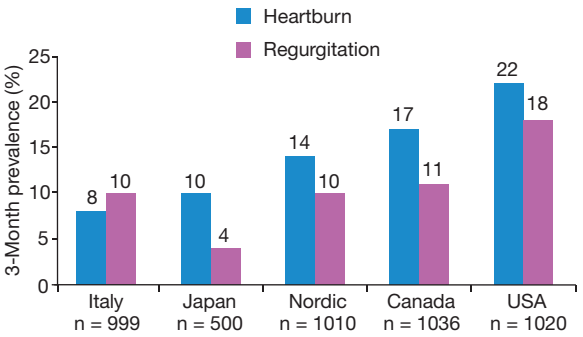

Fig. 7. Prevalence of gastroesophageal reflux disease worldwide. Note that the prevalence varies markedly from country to country, largely because of differences in physicians' awareness and understanding of the condition.

effects because, currently, proton pump inhibitors are among the most commonly prescribed and most expensive drugs.

PRESENTATION

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. GERD may contribute to many clinical syndromes, either as a common factor or a rare culprit (Table 2).

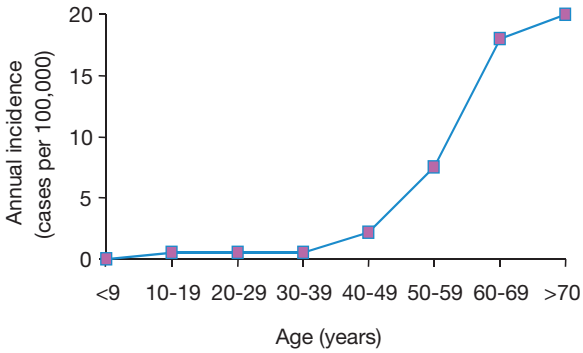

Fig. 8. Incidence of gastrointestinal reflux disease increases with age. Note that the incidence increases markedly after age 40 years. (From Brunnen PL, Karmody AM, Needham CD. Severe peptic oesophagitis. Gut. 1969;10:831-7. Used with permission.)

SYMPTOMS

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). This is 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 which is remasticated and again swallowed that typifies 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 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 (Fig. 10). 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

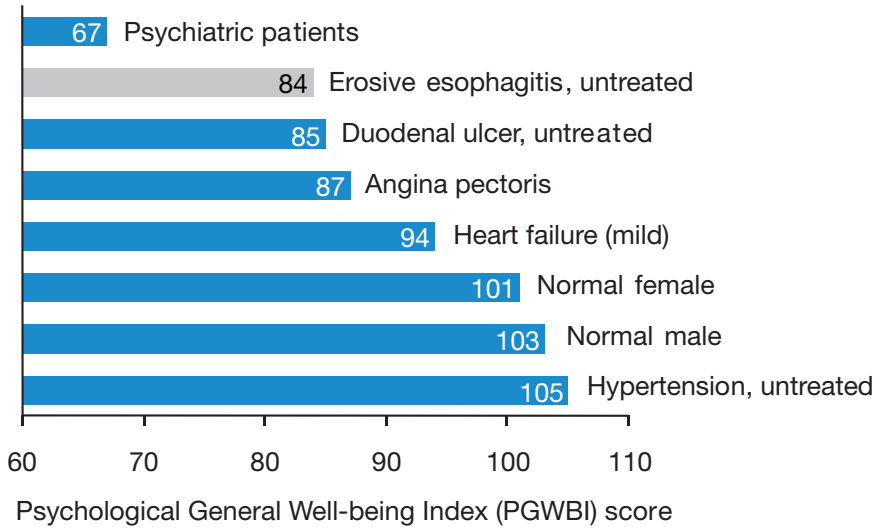

Fig. 9. Gastroesophageal reflux disease has a greater effect on quality of life than other common diseases. Quality of life, assessed by the PGWBI, was compared between patients with untreated gastroesophageal reflux disease and those with other disorders. For example, the mean PGWBI score of patients with untreated erosive esophagitis is similar to that of patients with untreated duodenal ulcer and lower (ie, worse) than that of 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. (Modified from Dimenäs E. Methodological aspects of evaluation of Quality of Life in upper gastrointestinal diseases. Scand J Gastroenterol Suppl. 1993;199:18-21. Used with permission.)

radiation to the neck, arm, or back. It may be indistinguishable from cardiac pain. Because of the potential fatal significance of cardiac 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.

Table 2. Symptoms of Gastroesophageal Reflux Disease

Esophageal symptoms
Heartburn
Acid regurgitation
Odynophagia
Dysphagia
Angina-like chest pain
Water brash (hypersalivation)
Airway symptoms
Cough
Wheezing
Hoarseness
Throat clearing
Globus
Tracheal stenosis
Aspiration pneumonia
Pulmonary fibrosis
Apnea in infants

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, or otalgia. They are not specific for GERD. Indeed, GERD is only one 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 empiric trial of potent acid-blocking therapy. Ideally, the

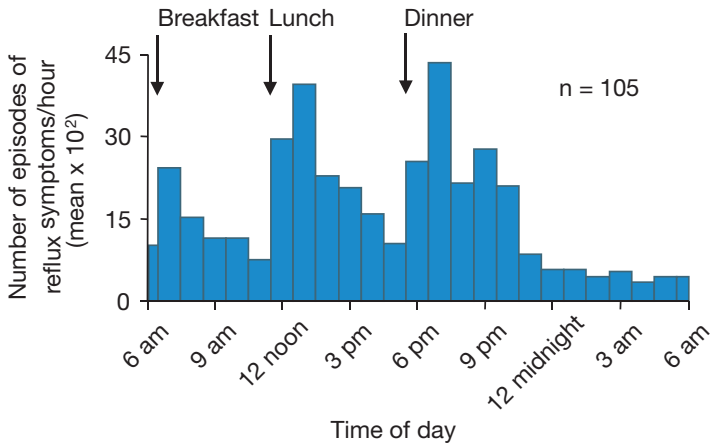

Fig. 10. Distribution of symptoms of gastroesophageal reflux disease over 24 hours in 105 patients who took their major meals at the same time of day. Note that food intake was associated with a marked increase in the number of symptom episodes and relatively few episodes occurred during the night. (From Johnsson L, Adlouni W, Johnsson F, Joelssson B. Timing of reflux symptoms and esophageal acid exposure. Gullet. 1992;2:58-62. Used with permission.)

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 one of two 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.

ESTABLISHING A DIAGNOSIS

Therapeutic Trial

Several studies have investigated the usefulness of empirical trials of acid-suppressive therapy with proton pump inhibitors (Table 3).

Typical Symptoms of Gastroesophageal Reflux Disease

Patients who present with typical symptoms without *alarm symptoms* should be given acid-supressive 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.

Table 3. Empiric Trials of Acid-Suppressive Therapy With Proton Pump Inhibitors for Diagnosis

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

**For the confirmation of gastroesophageal reflux disease.*

Atypical Symptoms of Gastroesophageal Reflux Disease

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 or hoarseness should be evaluated for asthma or laryngeal neoplasm, respectively. 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, for example, proton pump inhibitors (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.

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 GASTROESOPHAGEAL REFLUX DISEASE

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, and additional tests are required to identify increased esophageal exposure to acid. This is done either directly with ambulatory pH monitoring or indirectly by showing the reflux of a detectable material such as barium or a radiolabeled compound during a provocative maneuver or by reproducing symptoms through the instillation of acid (Table 4).

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 for various distances. The degree of severity varies. By their appearance alone, these erosions usually are readily differentiated from rarer infectious, allergic

Table 4. Uses of Diagnostic Tests for Gastroesophageal Reflux Disease

Endoscopy
Differentiate from other causes of reflux esophagitis
Biopsy Barrett's esophagus, adenocarcinoma
Dilate strictures
Endoscopic therapy (?)
Contrast radiography
Hiatal hernia
Identify strictures
Reproduce reflux of barium (?)
Ambulatory 24-hour pH studies
Quantify acid reflux in the absence of esophagitis
Determine temporal correlation between gastroesophageal reflux and atypical symptoms
Bernstein test
Provoke symptoms with acid
Gastroesophageal scintigraphy
Quantify gastroesophageal reflux
Identify aspiration

(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 (Fig. 11). 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's esophagus, and esophageal adenocarcinoma. Alarm 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. 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. In patients with extraesophageal symptoms, reflux of barium to or above the level of the aortic arch suggests the possibility of proximal reflux. 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. Its use is discouraged in the evaluation of uncomplicated GERD.

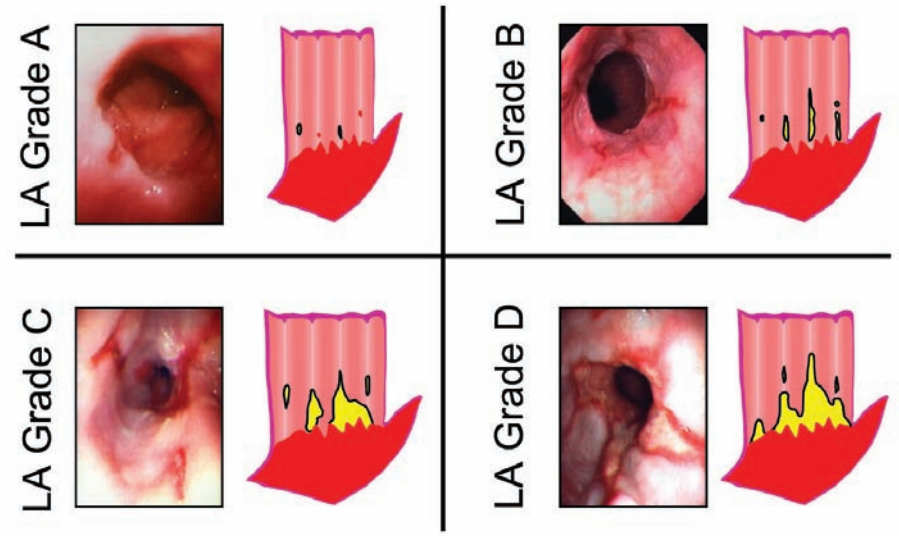

Fig. 11. Erosive esophagitis. Summary of Los Angeles (LA) classification. Grade A, one or more mucosal breaks not more than 5 mm in maximal length. Grade B, one or more mucosal breaks more than 5 mm in maximal length, but not continuous between the tops of two mucosal folds. Grade C, mucosal breaks that are continuous between the tops of two 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. (From AstraZeneca Pharmaceuticals LP [Internet]. Wilmington (DE). Available from: http://www.astrazeneca.com. Used with permission.)

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 Table 5. 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 stationary esophageal manometry study or with a combined single water-perfused pressure transducer with a pH probe that can locate accurately the proximal border of the sphincter and requires only a single intubation. Other methods such as 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. The patient should maintain his or her usual diet, activity, and habits during the study to allow the assessment of findings relative to the patient's 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.

Table 5. Indications for Ambulatory Esophageal pH Monitoring

Atypical symptoms: respiratory, ear, nose, and throat
Frequent atypical chest pain
Refractory symptoms in well-established GERD*
Preoperative confirmation of GERD

GERD, gastroesophageal reflux disease.
**Done on 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 (Fig. 12). *Reflux of acid* is defined as a sudden decrease in intraesophageal pH <4.0 that lasts longer than 5 seconds. The six most commonly reported measurements are 1) the percentage of total time that pH is <4.0, 2) the percentage of upright time that pH is <4.0, 3) the percentage of recumbent time that pH is <4.0, 4) the total number of reflux events, 5) the number of reflux episodes that last longer than 5 minutes, and 6) the longest episode of reflux (in minutes). The first three measurements of acid exposure are used most frequently in everyday practice, and 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 its ability to determine 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 to indicate 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

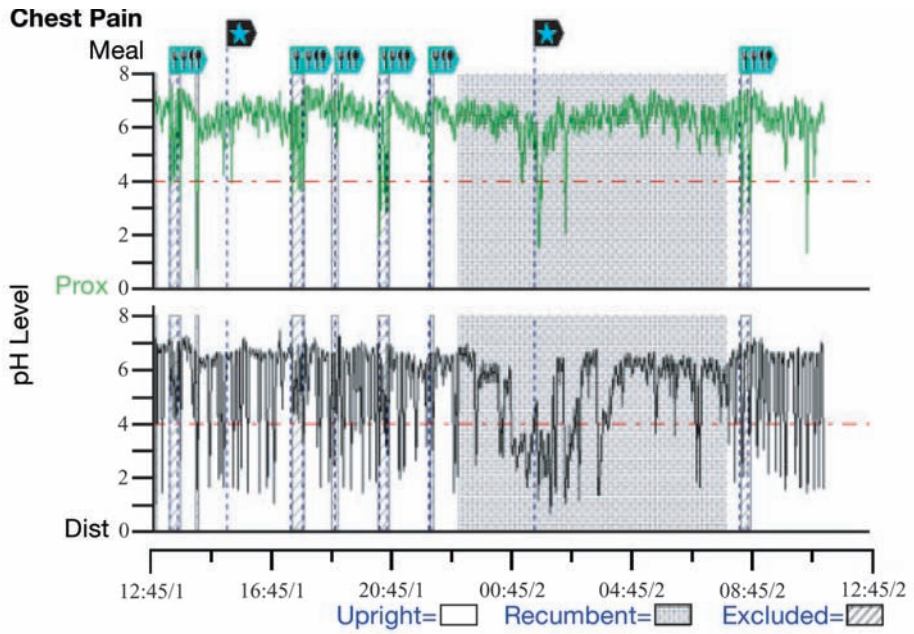

Fig. 12. Typical traces of 24-hour pH monitoring. The test was performed in a patient with chest pain. *Upper trace*, Electrode placed 20 cm above the lower esophageal sphincter. *Lower trace*, Electrode placed in the distal esophagus, 5 cm above the lower esophageal sphincter. Traces were recorded simultaneously. Esophageal pH must be <4 to be categorized as acid reflux. Marker flags, symptom episodes. Both episodes of chest pain (★) occurred during reflux episodes (symptom index = 100%). Abnormal upright and recumbent esophageal acid exposure occurs in the distal esophagus, suggesting both daytime and nightime reflux.

determine whether a temporal association exists depends on the number of symptom events and the amount of reflux that occurs. The patient must record his or her symptoms diligently and accurately during the study. If the symptoms occur once a week, 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 what is termed *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. A newer technique that measures both pH and intraluminal impedance may be able to detect nonacid reflux, but its role is not fully accepted and its clinical usefulness has not been demonstrated. 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.

Gastroesophageal Scintigraphy

Gastroesophageal scintigraphy is used rarely to demonstrate gastroesophageal reflux or aspiration. The technique involves feeding the patient a technetium 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, gross aspiration is needed). The test may be more useful in patients who have concomitant symptoms of delayed gastric emptying.

Bernstein Test

The Bernstein test is a provocative test in which acid (0.1N HCl) and water are infused alternately through a nasoesophageal tube into the midesophagus, with the patient unaware of the order of infusion. Of patients with GERD, 70% complain of heartburn within a few minutes after the start of the infusion of acid. Ideally, the symptom is relieved promptly when water is instilled. Because of low sensitivity and poor tolerance of the infusion, this test is not performed frequently. Great care must be taken to ensure that the tube is not in the airway, because instillation of acid into the lungs may have severe consequences.

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 6. 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. Perhaps there is partial improvement in symptoms. Although 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. 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.

Histamine$_2$ Receptor Blockers

Histamine$_2$ (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, nocturnal H_2 blockade does not produce sustained nocturnal acid suppression because of tachyphylaxis.

Proton Pump Inhibitors

Proton pump inhibitors are absorbed rapidly and taken up and concentrated preferentially in parietal cells. They irreversibly complex with the H^+-K^+-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 H_2 blockers as suppressors of acid reflux. The healing of esophagitis and the relief of 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.

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 is debated. 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. This approach is not recommended unless cost considerations are paramount.

Although routine doses of proton pump inhibitors (esomeprazole 40 mg/day, lansoprazole 30 mg/day, omeprazole 20 mg/day, pantoprazole 40 mg/day, rabeprazole 20 mg/day) are adequate for most patients with GERD, some 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 dose escalation or by adding a nocturnal H_2 blocker. However, the latter strategy 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 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.

With maintenance proton pump inhibitor therapy, the rate of relapse of esophagitis is 20%

Table 6. 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 hours before going to bed	
	Moderate size and fat content of meals	
	Loss of excess weight	
	Reduce intake of caffeine, chocolate	
	Stop smoking	
Acid neutralization	Antacids	20-30
	Chewing gum	
	Alginate preparations	
Acid suppression	H_2 blockers	50
	Proton pump inhibitors	≥80
Prokinetics	Metoclopramide (not useful)	30-40
	Others in development	
Mechanical prevention of reflux	Laparoscopic surgery	≥80
	Endoscopic therapies	≥50

or less, which is lower than for H_2 blockers (Fig. 13). A slight escalation 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. Although this has caused concern about a theoretical risk of carcinoid, the risk has not been realized after more than 10 years of long-term use of these agents. The increase in serum levels of gastrin and parietal cell mass may lead to rebound acid secretion after the therapy is stopped. The same effect also occurs, but for a shorter time, after H_2 blocker therapy is stopped. Epidemiologic studies have also raised the possibility of an association between proton pump inhibitor therapy and hip fractures.

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 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 withdrawn from use in the United States, and the long-term use of metoclopramide is associated with so many side effects that it is rarely prescribed for GERD unless that is incidental to its use for gastroparesis. Several prokinetic agents are being studied for the treatment of GERD, but the lower efficacy of prokinetics compared with that of proton pump inhibitors limits their potential usefulness. Drugs that target the TLESRs also have been used, including baclofen, which probably can reduce reflux but is not approved or 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 Table 7.

Functional Chest Pain

Many patients who complain the most bitterly of severe reflux often have very little reflux on 24-hour

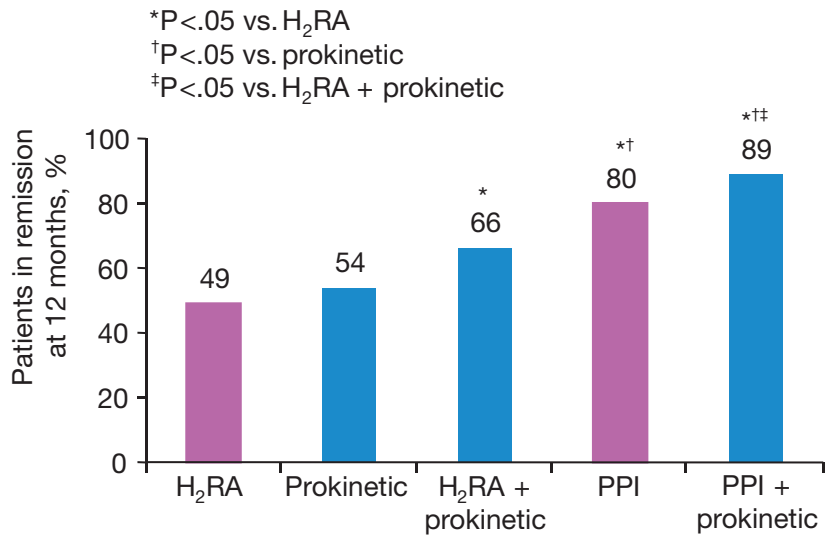

Fig. 13. Proton pump inhibitors (PPI) are the most effecive drugs for maintenance therapy of gastroesophageal reflux disease. Although the remission rate was slightly higher with PPI + prokinetic than with PPI alone, the difference was not significant. H_2RA, histamine$_2$ receptor antagonist. (Data 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;333:1106-10.)

pH monitoring and have no endoscopic features of reflux. This condition has been termed *nonerosive reflux disease*. As with other functional gastrointestinal tract problems, females 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, for example, 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 in fact are due 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,

Table 7. 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
Above diagnoses
Inadequate acid suppression
Noncompliance
Rapid metabolizers of proton pump inhibitors
Dose timing
Too low a dose
Zollinger-Ellison syndrome
Adenocarcinoma in Barrett's esophagus
Postoperative reflux—partial gastrectomy, vertical-banded gastroplasty
Esophageal dysmotility
Spasm
Achalasia
Nutcracker esophagus
Functional chest pain
Hypersensitive esophagus
Somatic features of depression
Free regurgitation
Absence of lower esophageal sphincter tone
Large hiatal hernia
Achalasia
Rumination

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 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.

Who Not to Send to Surgery

It would be prudent to reconsider carefully the wisdom of sending to surgery a patient who 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. Although some of these methods have been in clinical use, evidence for long-term efficacy is lacking.

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CHAPTER 2

Barrett's Esophagus and Esophageal Cancer

Yvonne Romero, MD

DEFINITIONS

Barrett's esophagus is the strongest risk factor known for esophageal adenocarcinoma (Fig. 1). Endoscopic and pathologic criteria need to be met to make the diagnosis of Barrett's esophagus. Endoscopy must demonstrate salmon-colored mucosa in the tubular esophagus (Fig. 2), and biopsy specimens must show intestinal metaplasia with goblet cells (so-called specialized intestinal metaplasia) (Fig. 3).

Arbitrarily, the term *long-segment Barrett's esophagus* refers to a salmon-colored segment of specialized intestinal metaplasia at least 3 cm long (Fig. 4). Essentially all the reports before 1985 refer to long-segment Barrett's esophagus. The term *short-segment Barrett's esophagus* refers to macroscopic segments or tongues of salmon-colored epithelium less than 3 cm in length seen at endoscopy (Fig. 4). Biopsy specimens from these segments show intestinal metaplasia with goblet cells. *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 (the so-called zig-zag line, or Z line) (Fig. 4). Currently, intestinal metaplasia of the cardia is *not* classified as Barrett's esophagus. Because the neoplastic risk of intestinal metaplasia of the cardia is thought to be low, the

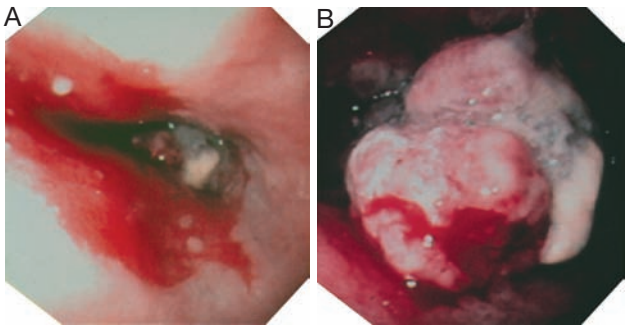

Fig. 1. Squamous epithelium, Barrett's esophagus, and the consequence: esophageal adenocarcinoma. *A*, Endoscopic view of three types of mucosa: icy pink squamous epithelium, salmon-colored mucosa, which is diagnostic of Barrett's esophagus if biopsy specimen shows intestinal metaplasia with goblet cells, and the mushroom-like growth of esophageal adenocarcinoma. *B*, Close-up view of exophytic esophageal adenocarcinoma in a field of Barrett's esophagus.

Abbreviations: CT, computed tomography; GERD, gastroesophageal reflux disease; PET, positron emission tomography.

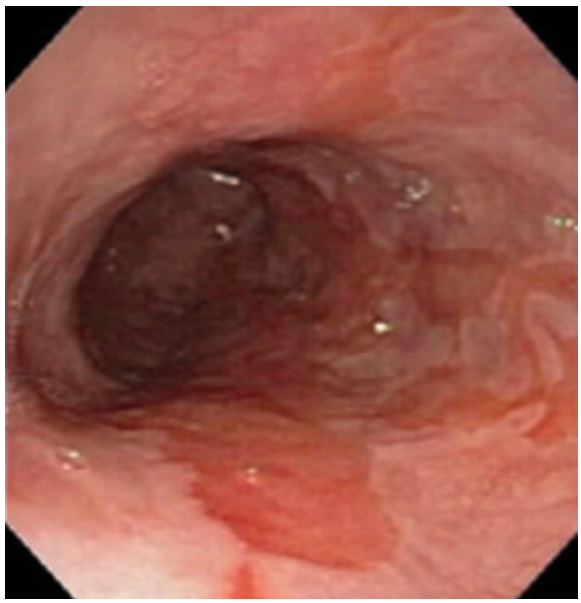

Fig. 2. Barrett's esophagus. (Courtesy of Drs. Kenneth K. Wang and Louis M. Wong Kee Song, Gastroenterology and Hepatology, Mayo Clinic.)

American Gastroenterology Association Chicago Workshop has advised that "the normal-appearing and normally located squamocolumnar junction should not be biopsied."

Pathophysiology

Barrett's esophagus is an acquired disorder in which columnar epithelium replaces the stratified squamous epithelium that normally lines the distal esophagus. This disorder is thought to occur in response to years of reflux of gastric contents into the distal esophagus. Hiatal hernias, weaker lower esophageal sphincter tone, and abnormal distal esophageal acid exposure, as measured with 24-hour pH testing, are more frequent in patients with Barrett's esophagus than in normal healthy controls and patients with erosive esophagitis. Currently, it is presumed that hiatal herniation and weak lower esophageal sphincter tone predispose to more severe reflux and chronic reflux initiates the metaplastic change from a squamous to a columnar epithelial lining. The length of the salmon-colored mucosal segment seen endoscopically does not change over time in patients with long-segment Barrett's esophagus. In one study, the segmental length remained constant in 21 patients who had repeat examinations at least 5 years apart (mean, 7.3 years). It is not clear if this is true also of short-segment Barrett's esophagus. With the common use of proton pump inhibitors and, thus, significant acid suppression, islands of squamous epithelium are often identified overlying Barrett's mucosa. These islands have not been shown to be clinically significant.

EPIDEMIOLOGY OF BARRETT'S ESOPHAGUS

Barrett's esophagus is associated with reflux symptoms, advancing age, male sex, and white race. To a much lesser extent, alcohol use and exposure to nicotine also are associated with Barrett's esophagus. The role of genetics and obesity is being investigated.

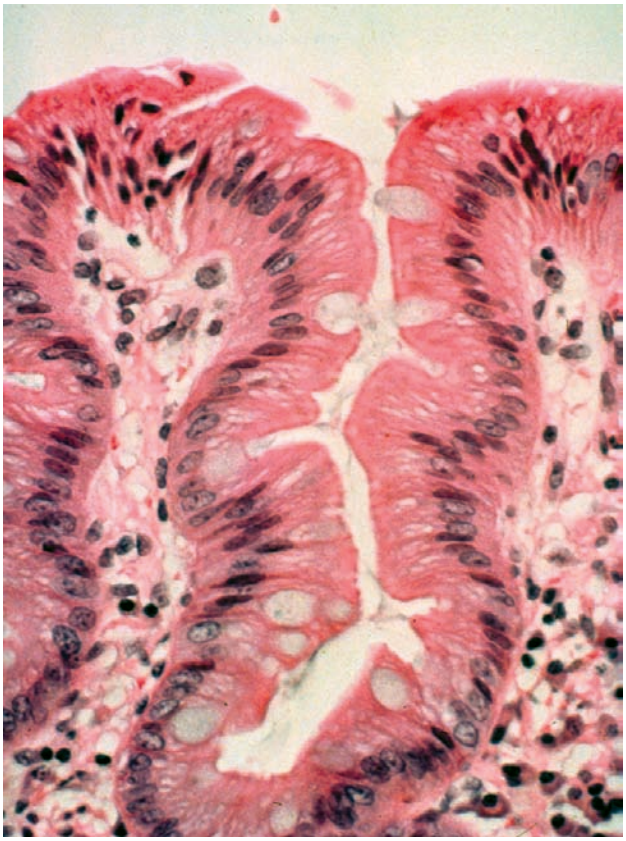

Fig. 3. Intestinal metaplasia with goblet cells. (Courtesy of Dr. Thomas C. Smyrk, Anatomic Pathology, Mayo Clinic.)

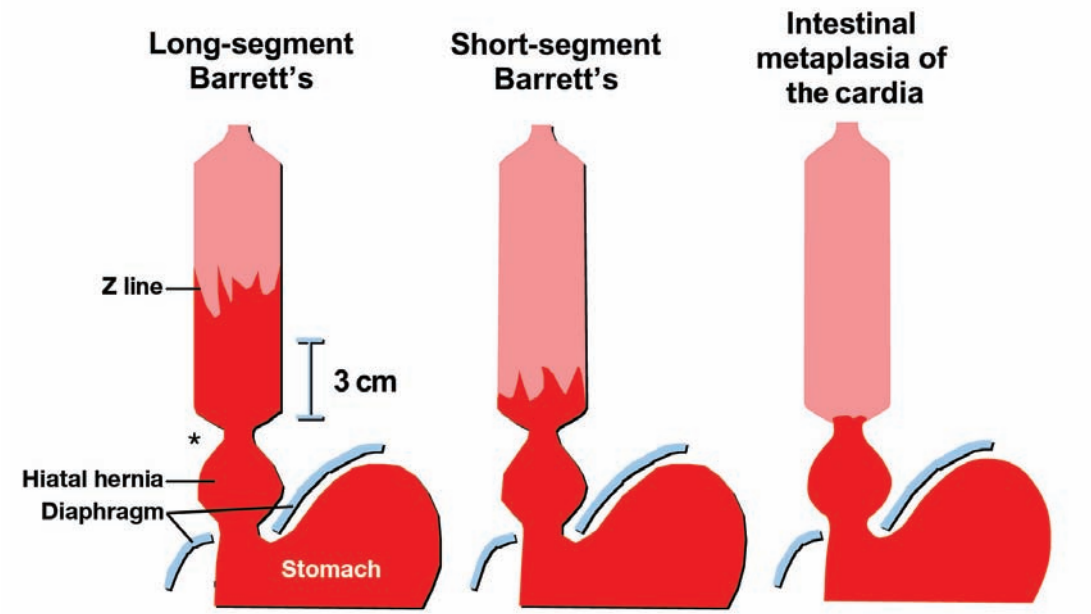

Fig. 4. Patients with long-segment or short-segment Barrett's esophagus have salmon-colored mucosa extending up into the tubular esophagus. Biopsy specimens must demonstrate intestinal metaplasia with goblet cells. If intestinal metaplasia with goblet cells is found at a normally located zig-zag line (Z line), the patient has intestinal metaplasia of the cardia, which confers a lower cancer risk. * End of tubular esophagus and beginning of stomach.

Prevalence of Barrett's Esophagus

The prevalence of Barrett's esophagus among whites of European background in developed countries does not appear to have changed remarkably over the past two decades. This statement is based on two landmark studies published in 1990 and 2005. The first study reported on Olmsted County, Minnesota, which has an enumerated population of predominantly Scandinavian, German, and others of European descent. The second study was from Sweden, whose populace is well enumerated. With enumerated populations, epidemiologic estimates can be calculated accurately because all the members are accounted for and the denominator is known.

In the 1980s, autopsy was performed on 37% of the residents who died in Olmsted County, Minnesota. The esophagi of autopsy specimens were examined prospectively over an 18-month period during 1986 and 1987. To confirm intestinal metaplasia with goblet cells, biopsy specimens were collected from esophagi that appeared to have at least 3 cm of salmon-colored mucosa. Thus, the prevalence of short-segment Barrett's esophagus and intestinal metaplasia of the cardia, concepts that were either nascent or nonexistent in 1986, was not determined. Of 733 consecutive unselected autopsies, 7 had long-segment Barrett's esophagus, giving a sex- and age-adjusted prevalence of long-segment Barrett's esophagus of 376 cases per 100,000 population, or 0.34%.

The prevalence of the combination of long-segment and short-segment Barrett's esophagus and intestinal metaplasia of the cardia was reported in 2005 in a Swedish population-based study involving two municipalities with a total population of 21,610. A validated symptom questionnaire was mailed to a random sample of 3,000 persons, and the response rate was 74%. A random subsample of 1,000 subjects who completed the questionnaire was invited to undergo upper endoscopy. Of these 1,000 people who had endoscopy, 5 were found to have intestinal metaplasia with goblet cells at least 2 cm in length, for an overall estimate of 0.5% with "longish" Barrett's esophagus. Because the authors did not report the prevalence of long-segment (≥3 cm) Barrett's esophagus, a direct comparison cannot be made with the 1987 autopsy data from Olmsted County, Minnesota. Nonetheless, both estimates are similar. The overall prevalence of Barrett's esophagus of any length, which included intestinal metaplasia of the cardia, was 1.6%.

Currently, in Olmsted County, Barrett's esophagus is diagnosed more frequently than it was in the past partly because more persons have endoscopy now than previously (Fig. 5). Also, endoscopists now probably are more aware of this clinical entity and, hence, less likely to overlook or miss it.

Although the number of people in whom Barrett's esophagus is being diagnosed has increased over the past 3 decades, this does not necessarily reflect a change in prevalence. The increase can be explained by two phenomena: increased recognition by physicians, especially of short-segment Barrett's esophagus, and increased detection because of increased use of diagnostic endoscopy (ie, the more endoscopic examinations performed, the more cases of Barrett's esophagus diagnosed). As seen in Figure 5, the first case of short-segment Barrett's esophagus was diagnosed in Olmsted County in 1985, not because short-segment Barrett's esophagus did not occur before 1985 but because it was not recognized as a disease before that time. In the early 1980s, it was common clinical practice to biopsy salmon-colored mucosa *only* if it extended 3 cm or more in length.

The number of new cases of long-segment Barrett's esophagus diagnosed per 100,000 population per year increased from 0.37 in 1965-1969 to 10.5 in 1995-1997, a 28-fold increase. During the same period, the number of upper endoscopic examinations performed on Olmsted County residents increased from 65 to 1,461 per 100,000 population per year, a 22-fold increase. Without knowing the denominator of persons undergoing endoscopy, one could erroneously conclude that the prevalence of Barrett's esophagus was increasing.

On the basis of the autopsy study described above, it was estimated that in 1987 in Olmsted County, Minnesota, for every 16 people with long-segment Barrett's esophagus, only 1 was aware of the disease. Thus, only 1 of 16 people with a preneoplastic condition had the opportunity to participate in a surveillance program. In 1998, this ratio was 1 in 7 in Olmsted County, likely because of open access endoscopy. For every seven people in Olmsted County with long-segment Barrett's esophagus, the disease has been diagnosed clinically in one and surveillance likely recommended. A recent systematic review has reported that fewer than 5% of patients who have both Barrett's esophagus and esophageal adenocarcinoma documented in a surgical resection specimen

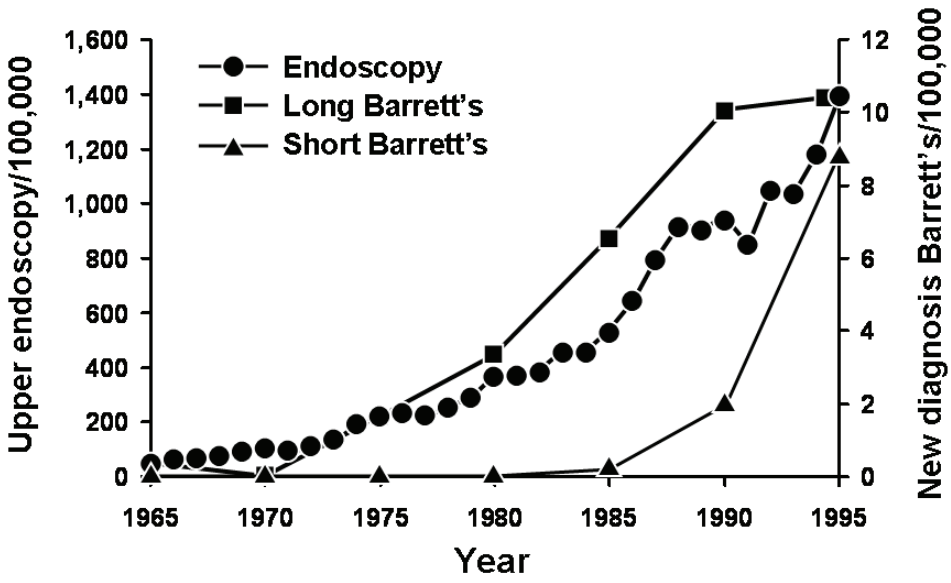

Fig. 5. Incidence of diagnosed long- and short-segment Barrett's esophagus and number of upper endoscopic examinations performed annually in residents of Olmsted County, Minnesota, from 1965 to 1995. (From Conio M, Cameron AJ, Romero Y, Branch CD, Schleck CD, Burgart LJ, et al. Secular trends in the epidemiology and outcome of Barrett's oesophagus in Olmsted County, Minnesota. Gut. 2001;48:304-9. Used with permission.)

had the diagnosis of Barrett's esophagus before seeking medical care for symptoms of cancer (dysphagia, weight loss of unclear origin, or anemia). It is unlikely that surveillance will be shown to be beneficial in decreasing the mortality rate of esophageal adenocarcinoma until Barrett's esophagus has been diagnosed in the majority of persons with this condition well in advance of progression to cancer. To date, case series have shown that patients with Barrett's esophagus in whom esophageal adenocarcinoma is diagnosed during routine surveillance are usually found to have earlier stage disease and longer survival than patients in whom Barrett's esophagus and cancer are diagnosed simultaneously. Because of the possibility of lead time bias in case series, it cannot be concluded confidently that surveillance increases survival. The hope is that once Barrett's esophagus has been diagnosed in all persons with the condition, trials can be conducted to assess the benefit, or lack of benefit, of surveillance.

Risk Factors for Barrett's Esophagus

Age

Barrett's esophagus is an acquired disorder. Thus, the prevalence of long-segment Barrett's esophagus increases with age (Fig. 6). The mean age at the time of clinical diagnosis is 63 years. Long-segment Barrett's esophagus is rare in children. A recent cohort study found that 8 of 166 children who received long-term proton pump inhibitor therapy had Barrett's esophagus, most commonly children older than 11 years who had altered mental status or another gastroesophageal reflux disease-predisposing disorder, such as Down's syndrome or cerebral palsy. Barrett's esophagus was exceedingly rare in children who had simple reflux disease.

Male Sex

In a Mayo Clinic study of patients who had endoscopy between 1976 and 1989, long-segment Barrett's esophagus was twice as common in males as in females. In a large multicenter Italian study (patients enrolled from 1987 to 1989), Barrett's esophagus was 2.6 times more common in males than in females. A higher male-to-female ratio has been reported also in studies of military populations in which females were in the extreme minority. In the 2005 Swedish population-based study, the male-to-female ratio of biopsy-proven Barrett's esophagus that was at least 2 cm in length was 1.5:1.

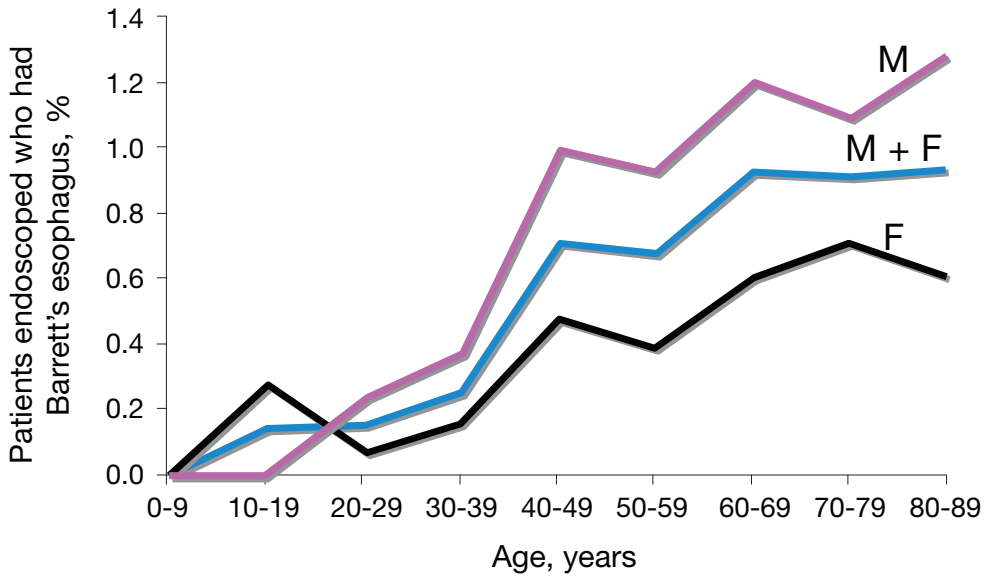

Fig. 6. Prevalence of Barrett's esophagus increased with age up to seventh decade. Half the maximum prevalence was reached by about age 40 years. Mean age at diagnosis was 63 years. F, females; M, males. (Courtesy of Dr. Alan J. Cameron, Emeritus, Mayo Clinic.)

Geography and Ethnicity

Long-segment Barrett's esophagus is described frequently in Western countries but appears to be less common in other countries, for example, Japan. In a recent single-center US retrospective cross-sectional cohort study of 2,100 people (37.7% white, 11.8% black, 22.2% Hispanic) who had endoscopy from 2005 to 2006, whites (6.1%) were more likely to have Barrett's esophagus of any length than blacks (1.6%, *P*=.004) or Hispanics (1.7%, *P*=.0002).

Reflux Symptoms

The symptoms of gastroesophageal reflux disease (GERD) include heartburn, which is described as substernal burning pain, and acid regurgitation, which is a bitter or sour taste that travels to the mouth. About 15% to 20% of adults in the United States report experiencing heartburn at least once a week, and 7% report daily symptoms. Of adults with symptoms of GERD, long-segment Barrett's esophagus is diagnosed at endoscopy in 3.5% to 7% (an age- and sex-adjusted estimate). In contrast, long-segment Barrett's esophagus is found at endoscopy in only 1% of adults who deny having symptoms of GERD.

Risk factor estimates for short-segment Barrett's esophagus are based mainly on cohort or case-control studies, which increase the possibility of overestimation of risk because of the limitations of study design. In a study in which all subjects reported heartburn at least twice a week, short-segment Barrett's esophagus was diagnosed in 7 of 378 (1.8%) consecutive patients who had endoscopy for various indications. In a case-control study, patients with short-segment Barrett's esophagus were more likely to have reflux symptoms than controls without this condition who had endoscopy for another indication.

Intestinal Metaplasia of the Cardia

Before 1994, biopsy specimens were not commonly collected from the normal-appearing zig-zag line (the junction of the cardia and the pale stratified squamous lining of the distal esophagus). It was presumed that biopsy specimens from this junction would show gastric cardia-type mucosa or, if the specimen was from an adjacent area, fundic mucosa. In 1994, Spechler et al reported on 143 consecutive patients who did not have endoscopic evidence of Barrett's esophagus but from whom biopsy specimens were obtained from the squamocolumnar junction according to protocol. Histologic evidence of intestinal metaplasia was found in 18% of these patients. Intestinal metaplasia with goblet cells at a normal-appearing Z-line has been demonstrated repeatedly by numerous investigators. For all patients who have endoscopy for any indication, the prevalence estimates range from 6% to 36%. The prevalence increases with age, suggesting that it is an acquired condition. However, unlike long-segment or short-segment Barrett's esophagus, intestinal metaplasia of the cardia is found equally in males and females and in whites and blacks, regardless of whether symptoms of GERD are present. Intestinal metaplasia of the stomach is associated with *Helicobacter pylori*. The role of *H. pylori* infection in the development of intestinal metaplasia of the cardia is being investigated.

CANCER RISK

Barrett's Esophagus

Reports of long-term follow-up of patients with long-segment Barrett's esophagus suggest that one cancer develops per 180 to 208 patient-years; that is, annually, esophageal adenocarcinoma develops in 0.5% of patients with Barrett's esophagus. Although a patient with Barrett's esophagus has a 30- to 125-fold higher risk of the disease progressing to adenocarcinoma than someone without this premalignant lining, the absolute risk of cancer is approximately 0.005 cancer per patient annually, which is exceedingly low. Thus, a 50-year-old man with Barrett's esophagus and otherwise normal life expectancy has a 3% to 10% lifetime risk (cumulative incidence) of developing esophageal adenocarcinoma.

The rate of neoplastic transformation is less for patients with shorter segments of specialized intestinal metaplasia. The findings from three series suggest that one cancer develops in short segments every 293 patient-years (ie, of 293 patients with 1 year of follow-up, 1 will have progression to esophageal adenocarcinoma). A study has demonstrated that the most important risk factor for predicting neoplastic progression is the degree of dysplasia and not the length of the Barrett's esophagus segment. Although length was not an independent risk factor for neoplastic progression, there was a trend toward significance, suggesting that perhaps this study was underpowered to address this specific outcome.

Because short-segment Barrett's esophagus is more common than long-segment Barrett's esophagus, the former is highly relevant from a societal perspective.

Intestinal Metaplasia of the Cardia

Esophageal adenocarcinoma is uncommon; approximately 7,000 cases were reported in the United States in 2007, at which time the country's population reached 300 million. For the general population, the prevalence of esophageal adenocarcinoma is 4 per 100,000 persons per year. This rate includes people with undiagnosed Barrett's esophagus who develop adenocarcinoma. Population follow-up studies of patients with intestinal metaplasia of the cardia are not available, but the practical conclusion seems clear. If one in five adults has intestinal metaplasia of the cardia, the risk that a single person with this finding will develop adenocarcinoma must be extremely small.

SURVEILLANCE

Because transformation to neoplasia depends more on the degree of dysplasia than on mucosal length, the current practice in the United States is to offer the same surveillance regimen to patients with short-segment or long-segment Barrett's esophagus. The guidelines of the American College of Gastroenterology recommend that the initial diagnostic endoscopic examination measure the proximal extent of salmon-colored mucosa and the distal end of the tubular esophagus–proximal extent of the gastric folds. Biopsy specimens are to be collected first from any suspicious lesions, for example, nodules, raised edges of an ulcer, or stricture. Thereafter, biopsy specimens are to be collected from every quadrant at 2-cm intervals along the length of the segment.

Currently, dysplasia is the best indicator of cancer risk. Surveillance endoscopy should be recommended to patients deemed eligible for intervention when an early lesion is identified. If no dysplasia is found at initial endoscopy, surveillance endoscopy is recommended in 1 year to exclude incident cancers or dysplasia. If no dysplasia is found at this examination, the surveillance interval can be extended to 3 to 5 years. If dysplasia of any degree is identified, with the exception of cancer, the Guidelines for the Diagnosis, Surveillance, and Therapy of Barrett's Esophagus, published in 2008 by the American College of Gastroenterology, recommend that additional acid-suppressive medications be administered before endoscopy is repeated. Inflammation commonly causes "reactive atypia," a cellular response to inflammation that easily can be overinterpreted as dysplasia. On repeat endoscopy, focused biopsy specimens should be collected from the level at which dysplasia was detected initially in addition to the usual four-quadrant biopsy specimens obtained at 2-cm intervals for follow-up of low-grade dysplasia or at 1-cm intervals for high-grade dysplasia. The American College of Gastroenterology has recommended consideration of endoscopic resection of the mucosa of any focal lesion to obtain more tissue for more accurate staging of disease. All slides should be reviewed by at least two gastrointestinal pathologists who are experts at staging Barrett's esophagus.

Low-Grade Dysplasia

If low-grade dysplasia is the most severe grade of dysplasia detected, a change in acid-suppressive regimen is recommended along with repeat endoscopy in 1 year. If low-grade dysplasia still persists, annual surveillance is recommended. If there is no evidence of dysplasia on two annual examinations, the surveillance endoscopy interval can be extended to 3 to 5 years.

High-Grade Dysplasia

If at least two gastrointestinal pathologists agree on the presence of focal high-grade dysplasia (dysplasia involving five or fewer crypts), four major options are available: 1) observation; 2) endoscopic mucosal resection, followed by photodynamic therapy; 3) photodynamic therapy alone; and 4) esophagectomy. The option of observation implies that the patient's acid-suppressive regimen will be altered and endoscopy will be performed every 3 months, at which time four-quadrant biopsy specimens will be collected at 1-cm intervals along the entire extent of the Barrett's segment. The observation option also implies that after frank cancer is found at biopsy, a more aggressive approach will be pursued. The American College of Gastroenterology has less confidence in the safety of simple observation for patients with multifocal high-grade dysplasia.

For decades, the standard of care for patients who have Barrett's esophagus with high-grade dysplasia or early stage I esophageal adenocarcinoma was esophagectomy. Endoscopic mucosal

resection is a technique in which epinephrine is injected submucosally beneath a nodule to raise it away from the circular muscle layers of the esophagus, thus diminishing the risk of perforation. This option is available for patients with high-grade dysplasia or early cancer in a nodule that is less than 2 cm in diameter and T1a (intramucosal) in depth. Endoscopic mucosal resection is commonly followed by photodynamic therapy administered to the remaining Barrett's mucosa. In patients without a nodular lesion, photodynamic therapy alone is administered. With photodynamic therapy, a systemically administered photosensitizer becomes concentrated in Barrett's mucosa and facilitates cell death when exposed to a particular wavelength of light administered at endoscopy. In 2007, a prospective cohort study showed that the 5-year survival for patients who had Barrett's esophagus with high-grade dysplasia or early stage I cancer was similar whether they had photodynamic therapy, with or without endoscopic mucosal resection, or esophagectomy. Consequently, photodynamic therapy, with or without endoscopic mucosal resection, is now considered a standard approach for selected patients who have Barrett's esophagus with high-grade dysplasia or early stage T1a (intramucosal) cancer. Because of patient hesitancy, a randomized controlled trial designed to compare directly endoscopic versus surgical therapy will likely never be performed.

Esophagectomy should be offered to physically fit patients. It is still the standard-of-care treatment option because it is the only treatment in which locoregional lymph nodes are removed. Patients interested in pursuing esophagectomy should be referred to a high-volume center. Perioperative mortality rates for this complex procedure vary greatly, from less than 3% to 20%, depending on the experience of the center.

Other treatment options under investigation include cryotherapy and radiofrequency ablation. However, because of the short-term follow-up of patients who have received these treatments, their use currently is considered experimental.

ESOPHAGEAL CANCER

Squamous cell carcinoma and adenocarcinoma are the most common types of esophageal cancer. Worldwide, esophageal cancer is the fifth most common type of gastrointestinal malignancy, most commonly, squamous cell carcinoma. In the United States, esophageal cancer is uncommon; approximately 14,000 cases are diagnosed annually, and since 2002, slightly more than half of these have been the adenocarcinoma type. The incidence of esophageal adenocarcinoma has been increasing exponentially over the past three decades for reasons that are unclear. Broadly speaking, the incidence of esophageal adenocarcinoma in the 1970s was 0.4 new cases/100,000 people per year. Currently, the incidence is 4 cases/100,000 people per year.

The incidence of squamous cell carcinoma in the United States is 2.6/100,000 people per year. In certain regions of China and Iran, squamous cell carcinoma is exceedingly common, occurring in 132 /100,000 people per year. This is thought to be related to environmental exposures.

Overall, neoplasms of the esophagus carry a poor prognosis. The 5-year overall survival rate ranges from 2% to 26%, depending on the stage at diagnosis.

Risk Factors for Squamous Cell Cancer

Several environmental risk factors are associated with squamous cell carcinoma, including the following: tobacco, alcohol, nitrosamines (eg, those generated by grilling meat), drinking scalding hot liquids and caustic substances (eg, lye), and chronic stasis (eg, that seen in patients with achalasia). Nutritional deficiencies, such as deficiency in vitamin C, and previous exposure to radiation, as in the treatment of Hodgkin's lymphoma or breast cancer, are also risk factors for squamous cell carcinoma. There is considerable geographic variation, with especially high incidence rates in some parts of China, Iran, and Afghanistan. The variation is thought more likely to be due to environmental, not genetic, factors because adjacent communities can have low incidence rates of cancer. However, several factors raise the possibility of a genetic component to squamous cell carcinoma, including the higher risk for blacks, or African Americans, than for whites and the strong association of squamous cell carcinoma with tylosis and a fair association with esophageal lichen planus.

Risk Factors for Adenocarcinoma

The risk factors for esophageal adenocarcinoma mirror the risk factors for Barrett's esophagus, and Barrett's esophagus is the strongest risk factor for

adenocarcinoma. Established risk factors for esophageal adenocarcinoma are advancing age, male sex, chronic reflux of gastric contents into the tubular esophagus, white ethnicity, and obesity. Heartburn and acid regurgitation, especially if present for more than 12 years, are also risk factors. The challenge is that 40% of patients with esophageal adenocarcinoma deny ever experiencing symptoms of GERD. Therefore, heartburn and acid regurgitation are helpful when present, but the lack of these symptoms does not mean the patient is not at risk for esophageal cancer.

Signs and Symptoms of Esophageal Cancer

The symptoms of esophageal cancer include new onset of solid food dysphagia that in a short time progresses to include dysphagia to soft solids and then liquids. Odynophagia, or painful swallowing, occurs either by ulceration directly from the tumor or secondarily from pill esophagitis. In some patients, the pain radiates to the midchest or back, especially during meals. 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 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 can be palpated.

Diagnosis and Staging

Esophageal cancers are staged to direct management and to inform prognosis. Two main components must be considered in therapeutic decision making: the patient's condition and the stage of disease. What is the patient's performance status? Is the patient an adequate surgical candidate? Does the patient have comorbid conditions that need to be addressed before an operation is considered? Is low-molecular-weight heparin appropriate? Does the patient have several comorbid conditions that will sway your recommendation away from surgery? Basically, stage is divided into early curable disease, advanced incurable disease, or something inbetween (Table 1).

Staging is usually performed in the following order: computed tomography (CT) of the chest and abdomen is performed first to screen for distant metastases. If CT findings are negative, positron emission tomography (PET) is recommended because it can detect unsuspected metastatic disease in 10% to 15% of cases, thus avoiding futile surgery. PET is superior to CT for detecting distant metastases but is more expensive and, hence, performed only if the CT findings are negative. If distant metastases are not found, the next step is endoscopic ultrasonography for locoregional staging (Fig. 7). If possible, it is most efficient to arrange for endoscopic mucosal resection at the time of endoscopic ultrasonography in case the tumor is found to be T1 in depth without suspicious lymphadenopathy. If tumor invasion is more advanced or lymph node involvement is documented with fine-needle aspiration, endoscopic mucosal resection can be cancelled. Mediastinoscopy and laparoscopy are rarely necessary to exclude carcinomatosis.

Consultations

Upon diagnosis of esophageal cancer, consultations should be considered with a gastroenterologist, medical oncologist, radiation oncologist, and thoracic surgeon. A team approach helps the patient learn the most about the disease, prognosis, and plethora of treatment options available for the stage of disease in the hope of achieving the best long-term outcome and optimal quality of life.

Table 1. Disease Extent, Treatment Options Based on Stage, and 5-Year Survival Rates by Stage

Disease extent	Stage	TNM classification	Treatment options	5-Year survival rate, %
Confined to esophageal wall	0 (high-grade dysplasia)	TisN0M0	a) Photodynamic therapy b) ± Endoscopic mucosal resection c) Esophagectomy	90
	I	$T1_{intramucosal}N0M0$	a) Photodynamic therapy b) ± Endoscopic mucosal resection c) Esophagectomy	50-70
	I	$T1_{submucosal}N0M0$	Esophagectomy	
	IIA	T2-T3N0M0	Esophagectomy	
Local lymph node involvement	IIB III	T1-T2N1M0 T3N1M0 T4N0M0 or T4N1M0	a) Definitive combination chemotherapy with radiotherapy b) Neoadjuvant combination chemoradiation therapy with restaging; if distant metastases are not demonstrated thereafter, esophagectomy	10-33
Celiac or supra-clavicular lymph node involvement	IVA	$T_{any}N_{any}M1a$	If in otherwise good health, consider definitive combination chemotherapy with radiotherapy	<5
Distant metastases	IVB	$T_{any}N_{any}M1b$	Palliation	<2

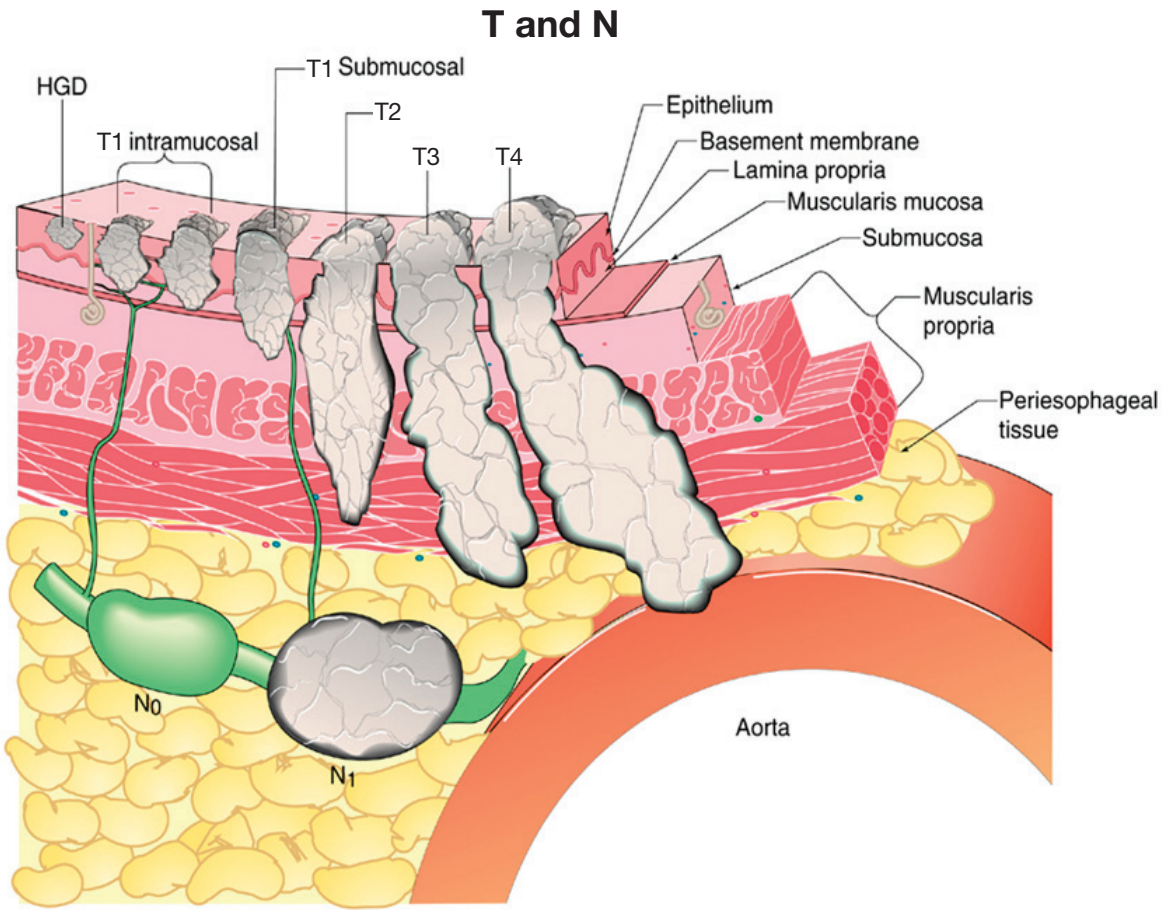

Fig. 7. T and N staging of high-grade dysplasia and esophageal cancer. HGD, high-grade dysplasia. (Courtesy of Dr. Thomas Rice, Thoracic and Cardiovascular Surgery, Cleveland Clinic.)

RECOMMENDED READING

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CHAPTER 3

Normal and Abnormal Esophageal Motility

Amindra S. Arora, MBBChir
Nicholas J. Talley, MD, PhD

Swallowing is a complex neuromuscular process that depends on motor and sensory innervation. The oropharyngeal phase of swallowing is under voluntary control. However, once the bolus has been moved into the pharynx, the process becomes involuntary, with the initiation of an integrated pattern of esophageal motor activity. Difficulty swallowing (*dysphagia*) can occur when the neuromuscular process is interrupted.

ANATOMY

Shaped like a funnel, the elastic pharynx joins the mouth to the esophagus and trachea. The upper esophagus consists of striated muscle. The *upper esophageal sphincter* (UES) consists of the cricopharyngeus muscle. The esophagus is a relatively simple neuromuscular tube that contains an inner circular layer of muscle and an outer longitudinal layer of muscle. Approximately at the level of the aortic arch, which is 22 to 24 cm from the incisors, the striated muscle begins to be replaced by smooth muscle in the *transition zone*. The lower 50% of the esophagus consists entirely of smooth muscle. A ring of thickened smooth muscle at the esophagogastric junction marks the *lower esophageal sphincter* (LES). Between swallows, the UES and LES protect from esophagopharyngeal and gastroesophageal reflux, respectively, because they keep the esophageal lumen closed.

Swallowing Physiology

After the lips are closed and the teeth are clenched, the tongue is elevated, anteriorly to posteriorly, against the palate, forcing the bolus to the pharynx. This initial process is under conscious control. However, entry of the bolus into the pharynx triggers the swallowing reflex, which is involuntary. The soft palate is elevated against the posterior pharyngeal wall, thus sealing the oropharynx and nasopharynx, and the larynx is elevated and the laryngeal inlet is closed, thus preventing 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 the peristaltic contraction of the pharyngeal muscles. As 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, the LES relaxes and remains relaxed

Abbreviations: GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; UES, upper esophageal sphincter.

until the bolus has entered the stomach, at which time the LES closes.

Relaxation of the LES occurs through the release of nitric oxide from myenteric neurons that innervate the LES. Myenteric neurons are also important in maintaining the resting basal tone of the upper esophagus. Peristaltic contractions are under local control of the myenteric plexus. The release of acetylcholine (excitatory effect) and nitric oxide (inhibitory effect) from neurons that supply the circular smooth muscle are involved in this process, which is activated by swallowing.

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 striated muscle in the proximal esophagus are innervated by cranial nerves IX (glossopharyngeal nerve) and X.

OROPHARYNGEAL DISORDERS

Disease that affects striated muscle causes oropharyngeal motor dysfunction and oropharyngeal dysphagia. These disorders can occur at the level of the muscle, the peripheral nerves, or the central nervous system.

To diagnose oropharyngeal dysphagia, consider the following important hints from the history:

- True dysphagia is present
- Food bolus transfer from the pharynx or hypopharynx is impaired (difficulty starting to swallow, food caught in the throat, unusual head or neck maneuvers during swallowing)
- Nasopharyngeal regurgitation is common (regurgitation of swallowed liquids through the nose)
- Aspiration is common (coughing or choking when swallowing, difficulty breathing when eating)

Neurologic disease can cause oropharyngeal incoordination, whereas muscle disease can result in weak pharyngeal contractions. The causes of oropharyngeal dysphagia are listed in Table 1.

Table 1. Causes of Oropharyngeal Dysphagia

Brain—cerebrovascular accident, head injury, Parkinson's disease, brainstem disease, multiple sclerosis, motor neuron disease, phenothiazines
Muscle or nerve—dermatomyositis, poliomyelitis, muscular dystrophies, myasthenia gravis
Cricopharyngeal dysfunction
Inadequate opening from fibrosis resulting in Zenker's diverticulum
Reduced muscle compliance leading to a cricopharyngeal bar

Investigations

Oropharyngeal dysphagia is assessed best with videofluoroscopy. For this test, patients swallow boluses of different texture. Ideally, the test should be conducted with the assistance of a speech pathologist working with a radiologist. The following can be identified with videofluoroscopy:

- An uncoordinated tongue, which will impair transmission of the bolus
- Soft palate dysfunction, which can lead to nasopharyngeal regurgitation
- Poor laryngeal closure, which can lead to aspiration
- Poor pharyngeal peristalsis, which results in residue in the valleculae or piriform sinuses

Identifying the presence of a cricopharyngeal bar is important. This is an indentation of the cricopharyngeal muscle that is seen as barium passes by slowly and the muscle relaxes poorly during swallowing. A cricopharyngeal bar can be the primary cause of oropharyngeal dysphagia in the absence of other neuromuscular disease, but the latter must be excluded. It is important to look for a pharyngeal or esophageal diverticulum (*Zenker's diverticulum*). This diverticulum is the result of abnormal opening of the UES and can be due to localized muscle disease. Most patients who present with Zenker's diverticulum are older than 50 years.

The presence of Zenker's diverticulum increases the risk of perforation by esophagogastroduodenoscopy or nasogastric tube

placement, so it is important that intubation be performed under direct vision if the history is suggestive of oropharyngeal dysphagia. This is another reason videofluoroscopy should be the initial test of choice.

Computed tomography of the neck can be helpful for excluding rare structural causes of oropharyngeal dysphagia, such as malignancy or cervical osteophytes. An ears-nose-throat evaluation may detect malignancy missed by other tests if the diagnosis is unclear. Esophageal manometry has a limited role and is generally unhelpful.

Treatment

The underlying neuromuscular disease, if present, should be treated. Speech therapy can be useful; learning new swallowing maneuvers can aid the process despite underlying abnormalities. If malnutrition is an issue and the patient has no improvement with speech therapy, placement of a percutaneous endoscopic gastrostomy tube should be considered. If Zenker's diverticulum is present, surgical diverticulectomy with UES myotomy is the treatment of choice. Endoscopic myotomy is an alternative to surgery; also, botulinum toxin can be injected into the UES.

ESOPHAGEAL DISORDERS

Disorders of esophageal motility can be identified with manometry. An example of a normal manometric recording of primary peristalsis is shown in Figure 1. After a water swallow, peristaltic progression occurs at a rate of 2 to 8 cm per second, followed by complete relaxation of the LES. The LES is tonically closed at rest, with a normal mean pressure of 20 mm Hg (range, 10-45 mm Hg). However, a water swallow can alter subsequent swallows for up to 20 to 30 seconds, so it is important to note the time intervals between the water swallows provided on a tracing. The normal distal wave amplitude is 30 to 180 mm Hg.

Clinical Assessment

Classically, patients with esophageal motility disorders present with dysphagia for both liquids and solids. Symptoms typically are intermittent. Chest pain is common.

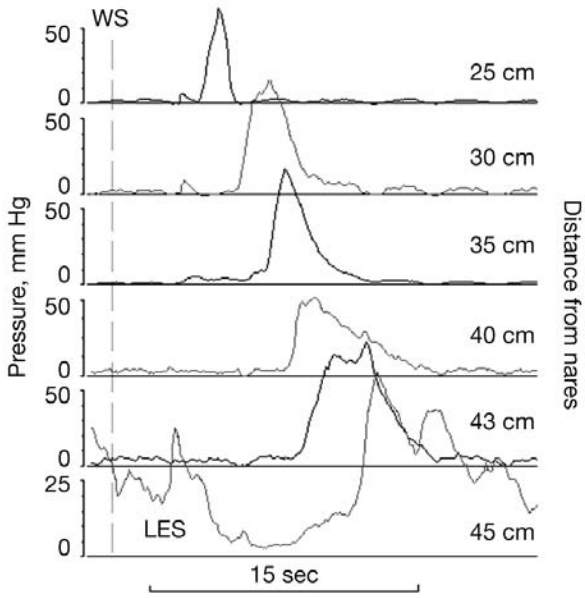

Fig. 1. Normal esophageal motor function. Manometric recording of normal esophageal peristalsis and relaxation of the lower esophageal sphincter (LES). The most distal sensor (bottom trace) is in the LES, which is defined as a region of increased pressure near the gastroesophageal junction that decreases with swallowing. A peristaltic sequence is recorded in the sensors above the LES. WS, occurrence of a wet swallow.

Classification of Esophageal Motility Disorders

A classification of esophageal motility disorders is summarized in Table 2.

Table 2. Esophageal Motility Disorders

Inadequate LES relaxation: achalasia (aperistalsis), atypical disorders
Uncoordinated contractions: diffuse esophageal spasm
Hypercontractile: nutcracker esophagus, isolated hypertensive LES
Hypocontractile: ineffective motility (nonspecific motility disorder)

LES, lower esophageal sphincter.
From Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. Gut. 2001;49:145-51. Used with permission.

Achalasia

Definition

Unlike most esophageal motility disorders, achalasia is a well-accepted neuropathic disease. *Achalasia* literally means "failure to relax." Its primary features are failure of peristalsis and failure of relaxation or incomplete relaxation of the LES.

Pathophysiology

The hallmark pathologic feature of achalasia is a decreased number of nonadrenergic, noncholinergic inhibitory ganglion cells. The cause of achalasia is unknown. Infection, especially varicella-zoster virus, has been implicated. A similar disease pathologically is Chagas' disease, which is due to infection by *Trypanosoma cruzi*. In Chagas' disease, a parasitic antigen that is similar to a protein on myenteric neurons produces an immunologic attack against the myenteric plexus.

Achalasia has a possible genetic component. Myenteric neuronal antibodies have been identified in up to 60% of patients with achalasia. However, whether this is an epiphenomenon or is causally related to the disease is unclear.

Clinical Presentation

Any age group can be affected by achalasia, but it typically occurs in the third to fifth decades. Men and women are affected equally. Often, there is a long history before the correct diagnosis is made. Virtually all patients have dysphagia for solids, and two-thirds of them have dysphagia for liquids. The dysphagia typically fluctuates, which is a hint. Regurgitation occurs in 60% to 90% of patients. Heartburn is common, not only from acid reflux but also from fermentation of food in the aperistaltic esophagus. Approximately one-third of patients report chest pain, although the mechanism is unclear. Weight loss may occur. Patients may have cough and pulmonary symptoms from aspiration.

Diagnosis

Barium swallow with fluoroscopy is an excellent screening test for achalasia. If the classic bird's beak appearance with a dilated esophagus is seen and typical symptoms are present, the diagnosis of achalasia is virtually certain (Fig. 2). However, pseudoachalasia needs to be actively excluded.

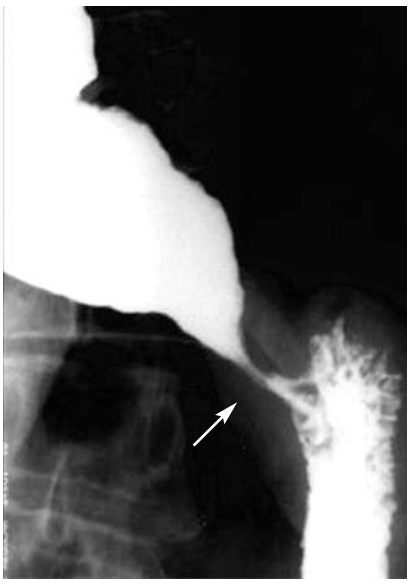

Fig. 2. Barium swallow study in a patient with achalasia. Note the dilated esophagus and tapering ("bird's beak") (*arrow*) at the gastroesophageal junction.

Manometrically, aperistalsis occurs with incomplete or failed relaxation of the LES after a swallow (Fig. 3). Increased LES pressure is common but not diagnostic. Low-amplitude simultaneous contractions

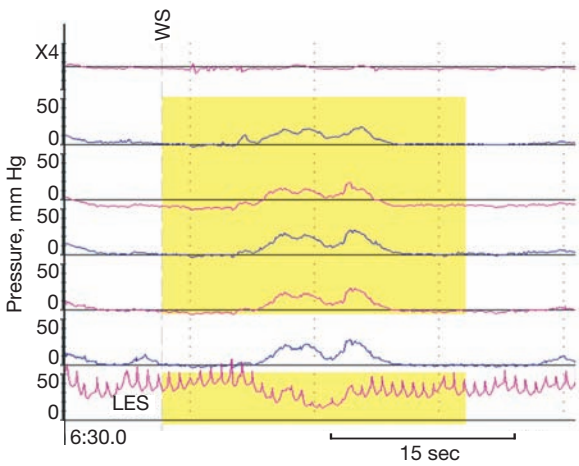

Fig. 3. Manometric recording from a patient with classic achalasia. The most distal sensor (bottom trace) is in the lower esophageal sphincter (LES). Note that the LES does not relax with wet swallows (WS). Wet swallows do not produce peristaltic pressure waves in the esophagus; instead, there are low-amplitude, simultaneous pressure waves with a nearly identical configuration.

may be seen. Intraesophageal pressure usually is increased because the esophagus is behaving as a common cavity. Consider the esophagus as though it were a sausage-shaped balloon filled with either liquid or air and containing a manometry catheter. If you squeeze the balloon anywhere (without blocking the lumen), an increase in pressure will be recorded nearly everywhere simultaneously in the balloon. In vigorous achalasia, simultaneous repetitive high-amplitude contractions occur in the esophagus. However, this manometric change does not have any clear clinical correlate.

Differential Diagnosis

It is essential to exclude malignancy-causing pseudoachalasia. This can occur from infiltration of the neural plexus directly by tumor, from a large constricting mass in the esophagus, or, rarely, from antineuronal nuclear autoantibodies, for example, as in a paraneoplastic syndrome, often in association with small cell lung cancer. Manometry cannot distinguish between pseudoachalasia and achalasia. Although presentation at older age, short duration of symptoms, and rapid weight loss all suggest pseudoachalasia, the history alone is insufficient for making the diagnosis. Endoscopy is essential in examining for evidence of malignancy. Other conditions that can cause pseudoachalasia include amyloidosis, sarcoidosis, postvagotomy, chronic intestinal pseudo-obstruction, neurofibromatosis, and even pancreatic pseudocyst.

Management

The four major options for management are drugs, botulinum toxin, pneumatic dilatation, and surgical myotomy.

Drugs

All drugs for achalasia have very limited efficacy. Nifedipine (10-30 mg), a calcium channel antagonist, was shown in a small crossover trial of 10 patients to reduce dysphagia and LES pressure in achalasia, although the overall results were not impressive. Sublingual isosorbide dinitrate (a nitric oxide donor) can relax the LES. Sildenafil (which increases cyclic guanosine monophosphate) also may have some benefit for LES relaxation.

Botulinum Toxin

Injection of botulinum toxin into the LES is effective. The toxin binds to the presynaptic cholinergic receptors and inhibits the release of acetylcholine from the presynaptic terminals of the neuromuscular junctions. The injection decreases LES pressure by more than 30% and induces a clinical response in 60% to 75% of patients. However, symptoms usually recur within 3 to 12 months, leading to the need for repeated injections. Furthermore, antibodies develop against the botulinum toxin, usually resulting in its loss of efficacy. Although botulinum toxin can cause fibrosis, pain, or rash after injection, it generally is well tolerated. This treatment is not a contraindication to surgery even though it potentially can cause tissue reactions that obscure fascial planes. Botulinum toxin is a useful option for "buying time" in achalasia, if this is needed. It is the optimal approach for frail elderly patients who are not candidates for surgery or pneumatic dilatation.

Pneumatic Dilatation

Pneumatic dilatation has more than a 60% and up to a 90% good response rate in achalasia. The forceful dilatation disrupts the LES, and this is believed to be the mechanism producing the benefit. If patients do not have a response to a second dilatation, they are less likely to have a response to additional dilatations, but some physicians attempt pneumatic dilatation one more time after other options have been discussed with the patient. The response tends to be better in patients who are older and have a long history of achalasia. The poorest response occurs if patients are younger than 40 years and the postdilatation LES pressure is more than 20 mm Hg.

Treatment should begin with the smallest (3-cm diameter) achalasia balloon (eg, Microvasive Rigiflex). The dilatation should be performed under fluoroscopic guidance. The balloon should be inflated gradually until the indentation at the esophagogastric junction is obliterated (7-10 psi) for 60 seconds. If dysphagia has not improved in 4 to 8 weeks, then a 3.5-cm balloon should be used. The largest balloon is 4 cm.

A major disadvantage of pneumatic dilatation is the risk of complications. The reported rate of esophageal perforation is approximately 3%, with

one-half of the patients requiring surgical repair. The overall procedure mortality rate is less than 0.5%. Because of this risk, it is important to give water-soluble contrast after dilatation and observe patients for 6 hours before discharge. Small contained perforations can be treated conservatively by not allowing any oral intake and administering antibiotics and by close observation with a surgical colleague. Gastroesophageal reflux disease (GERD) can develop after pneumatic dilatation (3%-15% of patients). After a patient has pneumatic dilatation, annual quantitative barium esophageal studies can be useful to quantify esophageal emptying.

Standard bougienage has been compared with pneumatic dilatation in a study of 18 patients with Chagas' disease. The results suggested that dilatation of the esophagus by bougienage has no long-term value, although patients may report brief improvement of symptoms.

Surgical Myotomy, Open or Laparoscopic

Currently, laparoscopic surgical myotomy is the procedure of choice. The previous use of botulinum toxin or pneumatic dilatation is not a contraindication to surgery. Data suggest that patients have the best symptom response rate (90%) and durability with surgery. Postoperatively, up to one-half of patients may require acid suppression for GERD.

If dysphagia recurs after being treated successfully with pneumatic dilatation or surgery, the literature provides little guidance about the optimal next step in management. However, pneumatic dilatation or repeat myotomy can be performed after myotomy fails, with a success rate better than 50%. In very severe disease unresponsive to all the above-mentioned approaches, esophagectomy is the only option.

Long-term Outcome

Patients with achalasia have a slight increase in the risk of squamous cell carcinoma. However, routine surveillance is not standard practice. If new or worsening dysphagia develops in a patient who has a history of achalasia, upper endoscopy should be repeated. Aspiration pneumonia is a well-recognized complication of achalasia.

Esophageal Spastic Disorders

Diffuse Esophageal Spasm

This is a relatively rare disease, and the manometric findings correlate poorly with symptoms. Approximately 3% to 10% of patients with noncardiac chest pain or unexplained dysphagia may have esophageal spasm. In about 3% to 5% of patients, esophageal spasm progresses to achalasia. Diffuse esophageal spasm may improve spontaneously in some patients during follow-up. Whether esophageal spasm results from an imbalance of inhibitory and excitatory motor innervation of the esophagus is unclear.

The esophagogram may be abnormal (Fig. 4), but manometry is usually required to make the diagnosis. The manometric definition of esophageal spasm is that more than 30% of wet swallows have simultaneous pressure waves (Fig. 5). A prolonged pressure wave (>6 seconds) of the wet swallow, normal peristalsis, and normal relaxation of the LES support the diagnosis. Vigorous achalasia is a combination of diffuse esophageal spasm and failure of the LES to relax.

Nutcracker Esophagus

This manometric condition is characterized by high-pressure (>180 mm Hg) peristaltic contractions.

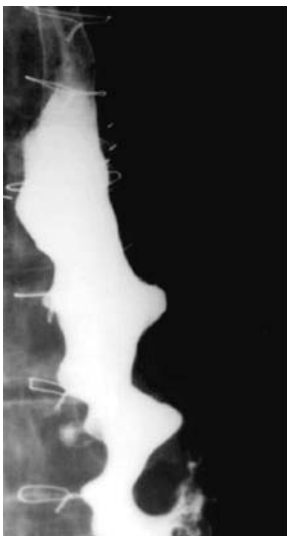

Fig. 4. Barium swallow study in a patient with diffuse esophageal spasm. Note the irregular border of the esophagus ("corkscrew esophagus"), suggesting uncoordinated contractile activity.

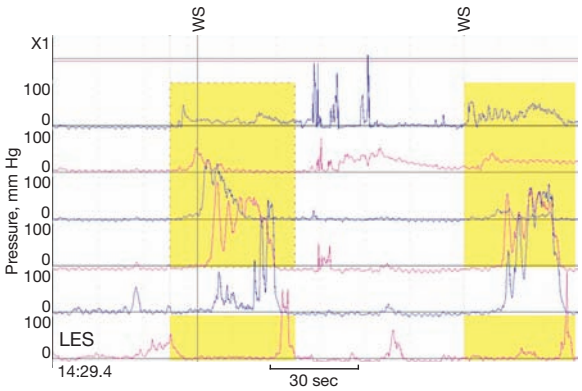

Fig. 5. Manometric recording from a patient with diffuse esophageal spasm. The most distal sensor (bottom trace) is in the lower esophageal sphincter (LES). WS, occurrence of a wet swallow.

Importantly, the peristaltic contractions propagate normally in the esophagus; also, the LES relaxes normally. It is unclear whether this is a "real" disease.

Treatment

In a crossover study of 22 patients with nutcracker esophagus, diltiazem (60-90 mg 4 times daily) versus placebo was tested. Diltiazem significantly lowered mean distal esophageal peristaltic pressure compared with placebo and also had a tendency to reduce chest pain scores, but the results were not impressive. Use of other therapies for esophageal spastic disorders is largely anecdotal. Nitrates and sildenafil may provide some benefit. Tricyclic antidepressants may reduce noncardiac chest pain, but this is irrespective of the underlying manometric findings (which may reflect that the manometric findings are irrelevant). In uncontrolled studies, botulinum toxin has been helpful.

Spastic esophageal disorders can be triggered by underlying GERD. Thus, aggressive treatment of documented gastroesophageal reflux is reasonable. Pneumatic dilatation of the esophagus has not been shown to improve diffuse esophageal spasm. Long myotomy for refractory diffuse esophageal spasm is effective in 50% to 70% of patients.

Hypomotility of the Esophagus

This is characterized by a decreased or absent resting LES and reduced or absent peristaltic wave pressures. Sometimes it is difficult to distinguish between esophageal hypomotility and achalasia. Scleroderma and other connective tissue diseases can present with esophageal hypomotility (Fig. 6). Muscular dystrophies and familial visceral myopathies also may present in this way.

Nonspecific Esophageal Motor Abnormality

In the esophageal manometry laboratory, about one-half of the patients with dysphagia have nonspecific motor abnormalities, which may or may not occur in relation to reflux disease. These abnormalities are not associated with dysphagia and are not specific. Diseases such as diabetes mellitus, amyloidosis, or hypothyroidism can be associated with a nonspecific esophageal motor abnormality.

Eosinophilic Esophagitis

Patients presenting with unexplained solid-food dysphagia or intermittent food impaction may have eosinophilic esophagitis. This is most common in young, typically male patients who do not have symptoms of GERD. Endoscopic examination may show a corrugated ("ringed") esophagus, particularly in the proximal middle esophageal region. Increased intraepithelial eosinophils (>20/high-power field) are seen in biopsy specimens. There are no distinct underlying esophageal motility findings, although abnormalities may be seen on manometry. Many adult patients have a response

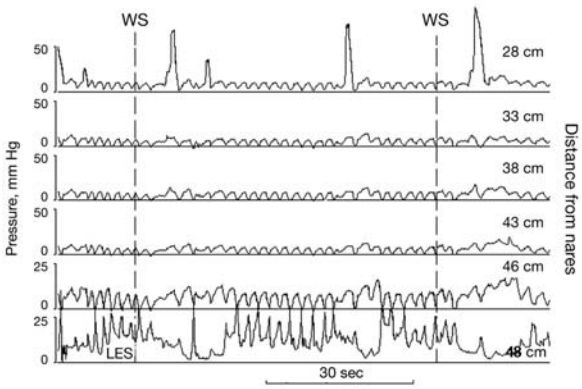

Fig. 6. Manometric recording from a patient with scleroderma. The most distal sensor (bottom trace) is in the lower esophageal sphincter (LES). Typical manometric findings of scleroderma include low-amplitude or absent peristaltic pressure waves in the smooth muscle part of the esophagus and a low-pressure LES. Generally, the striated muscle part of the esophagus (top trace) functions normally. WS, occurrence of a wet swallow.

to corticosteroids applied topically for 6 weeks. Montelukast also has been used successfully.

Post-Fundoplication 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. Also, the intrabolus pressure may increase just before the peristaltic pressure wave ("proximal escape") (Fig. 7). Dilatation of the esophagus for persistent dysphagia after fundoplication can be helpful.

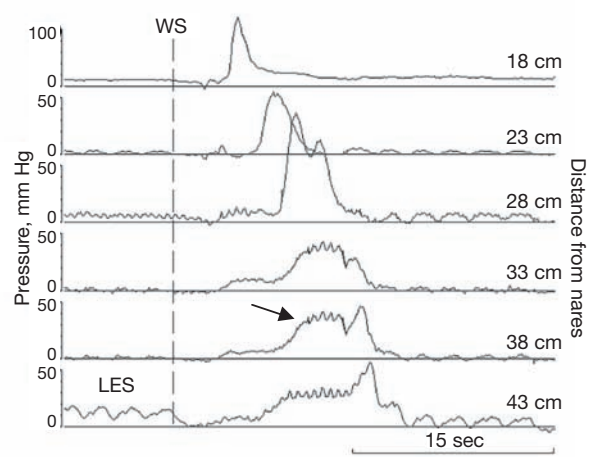

Fig. 7. Manometric recording from a patient with Nissen fundoplication. All the sensors are within the esophagus. Note that in the distal esophagus the pressure waves are biphasic. The first pressure wave (*arrow*) is the pressure in the bolus, preceding the peristaltic contraction; this is the intrabolus pressure. The second is the pressure wave accompanying the peristaltic contraction. Normally, the intrabolus pressure is seen during esophageal manometry, but it is of lower amplitude. The intrabolus pressure in this example is increased because of the distal esophageal obstruction produced by a tight fundoplication. LES, lower esophageal sphincter; WS, occurrence of a wet swallow.

SUMMARY

Generally, asymptomatic esophageal manometric findings should be ignored. Achalasia is the best established esophageal motility disorder. Most other esophageal motility disorders have questionable associations with clinical presentations. GERD is a common cause of dysphagia, and this can be secondary to motor dysfunction. Disorders of the UES produce oropharyngeal dysphagia, which clinically is quite distinct from the symptoms of distal esophageal motor disorders. An algorithm for assessing dysphagia is given in Figure 8.

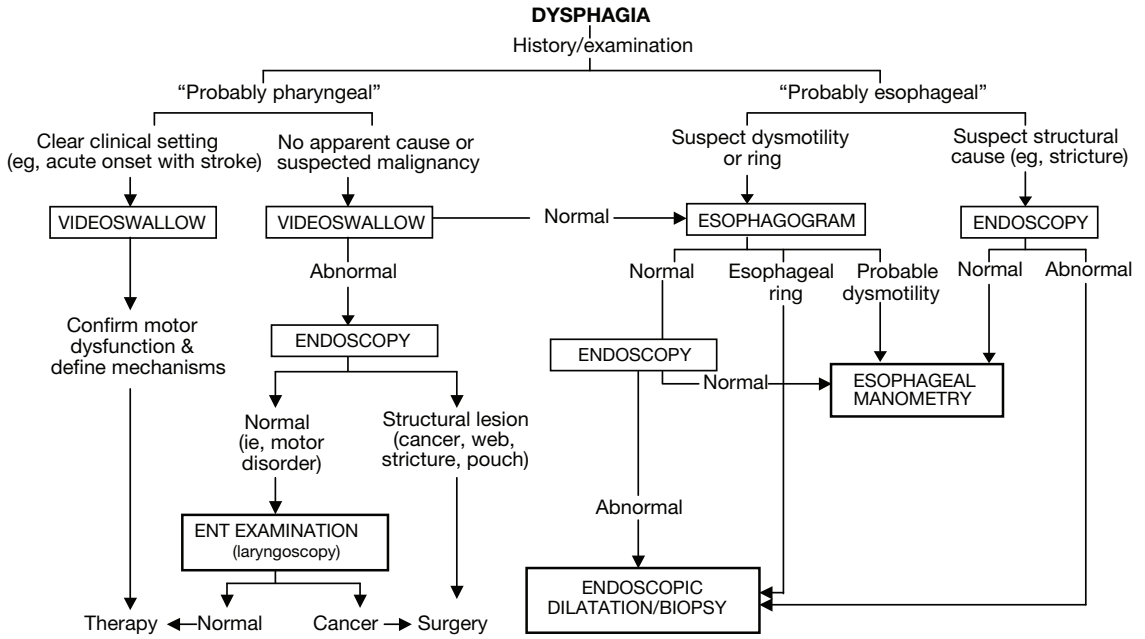

Fig. 8. Management of dysphagia. ENT, ears-nose-throat. (Modified from Cook IJ. Difficulty swallowing and pain on swallowing. In: Talley NJ, Martin CJ, editors. Clinical gastroenterology: a practical problem-based approach. 2nd ed. Sydney (Australia): Elsevier; 2006. p. 20-35. Used with permission.)

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Esophagus

Questions and Answers

QUESTIONS

Abbreviations used:
CT, computed tomography
EGD, esophagogastroduodenoscopy
GERD, gastroesophageal reflux disease
LES, lower esophageal sphincter
PET, positron emission tomography
PPI, proton pump inhibitor

Multiple Choice (choose the best answer)

1. During an endoscopic examination to evaluate diarrhea in a 63-year-old man, mild Los Angeles Classification System Grade A reflux esophagitis, small hiatal hernia, and a 2-cm segment of Barrett's esophagus with low-grade dysplasia were diagnosed. He is referred to you for management. He has researched Barrett's esophagus on the Internet and is very unhappy with the diagnosis of a premalignant disorder. He requests an intervention to prevent the progression to cancer. He states that he has not experienced heartburn, acid regurgitation, dysphagia, and unintentional weight loss. You recommend:

a. PPI therapy for 6 months before repeat endoscopy
b. Surveillance endoscopy in 6 months
c. Photodynamic therapy
d. Fundoplication
e. Esophagectomy

2. A 75-year-old male swimmer with a 10-cm segment of Barrett's esophagus is found at surveillance endoscopy to have a 3-cm area of nodularity at the proximal aspect of the Barrett's segment. Six biopsy specimens from the nodular region show high-grade dysplasia, as confirmed by two gastrointestinal pathologists. Biopsy specimens from the remaining Barrett's segment show high-grade dysplasia at the most distal aspect. Otherwise, biopsy specimens show diffuse low-grade dysplasia. He has been taking a PPI for 7 years and is symptomatically well. Chest and abdominal CT scans are without lymphadenopathy. There are no suspicious lesions in the lungs or liver. The results of cardiac stress testing are normal. Both of the patient's parents lived well into their 90s, and he has always planned to do the same. For treatment, you recommend:

a. Alteration of the PPI regimen, followed by repeat EGD in 3 months, with four-quadrant biopsy specimens collected every 1 cm
b. Endoscopic mucosal resection
c. Endoscopic mucosal resection, followed by photodynamic therapy
d. Photodynamic therapy
e. Esophagectomy

3. Because of a family history of Barrett's esophagus, a 67-year-old white man with rare GERD symptoms of 20 years' duration presents for

endoscopy. He states that he does not have dysphagia or unintentional weight loss. At upper endoscopy, he is found to have a 5-cm segment of Barrett's esophagus, with a 2-cm polypoid nodule present at the proximal aspect of the segment. Biopsy results show adenocarcinoma. He has stable coronary artery disease and hypertension. CT of the chest and abdomen and PET findings are negative for distant metastases. Endoscopic ultrasonography shows the lesion to be T2N0. You recommend:

a. Endoscopic mucosal resection with photodynamic therapy
b. Esophagectomy
c. Neoadjuvant combination chemoradiation therapy, followed by esophagectomy
d. Esophagectomy, followed by adjuvant chemotherapy
e. Definitive combination chemoradiation therapy

4. A 50-year-old African American woman has rheumatoid arthritis, class IV ischemic cardiomyopathy, and rheumatoid restrictive pulmonary disease requiring nocturnal oxygen supplementation. She informs her rheumatologist that her weekly heartburn and rare nocturnal regurgitation of 20 years' duration have worsened over the past 2 months. She has new nonspecific substernal chest pain with mild odynophagia. She states that she does not have dysphagia, impaction, or unintentional weight loss. She is a nonsmoker. She has taken famotidine at bedtime for 10 years. No changes have been found in her cardiac status. Her rheumatologist refers her to you. She has never had EGD. You recommend:

a. Upper gastrointestinal barium swallow
b. Esophageal capsule study
c. EGD
d. Empiric treatment with a PPI
e. Surgical consultation

5. One month ago, during upper endoscopy performed to investigate iron deficiency anemia, Barrett's esophagus of unknown length was diagnosed in a 35-year-old woman who did not have heartburn, acid regurgitation, dysphagia, or upper respiratory tract symptoms. She has been referred to you for management. The slides have been reviewed by your pathologist, who confirms the presence of intestinal metaplasia with goblet cells, without dysplasia. You recommend:

a. A prescribed PPI
b. An over-the-counter PPI
c. Fundoplication
d. Repeat endoscopy now
e. Repeat endoscopy in 1 year

6. A 62-year-old woman with intermittent chest pains and dysphagia comes to your office with a report from an outside institution, following an esophageal motility test. The test report is as follows: "The lower esophageal sphincter pressure was elevated at 52 mm Hg (normal 10-45) and, after wet swallows, there was a failure of complete relaxation to the gastric baseline." Five of the 10 wet swallows were peristaltic and five wet swallows were simultaneous. What is the most likely diagnosis?

a. Scleroderma
b. Achalasia
c. Diffuse esophageal spasm
d. Nutcracker esophagus
e. Nonspecific motility disorder

7. A 42-year-old man with a 7-year history of regurgitation and heartburn has come to you because of worsening symptoms. He describes difficulty getting food down (both liquids and solids). Also, when he bends down, he occasionally regurgitates all food. He has had to elevate the head of his bed. A barium swallow study was performed.

Question 7

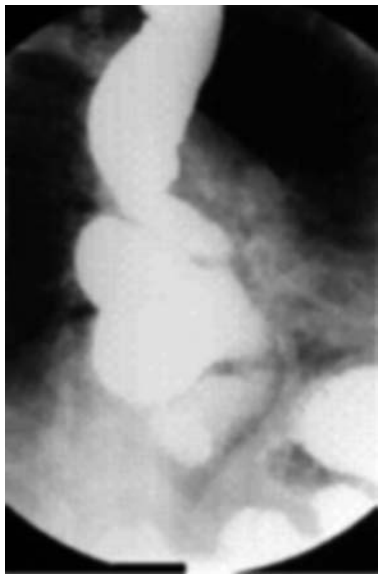
The most likely diagnosis is:

a. Scleroderma
b. Achalasia
c. Diffuse esophageal spasm
d. Nutcracker esophagus

8. A 52-year-old man has at least a 6-month history of progressive dysphagia. He has difficulty swallowing both liquids and solids. On physical examination, some fasciculation of the tongue is noted. The most appropriate test to order to evaluate this man's dysphagia would be:

a. EGD
b. Video swallow
c. Esophageal manometry
d. Ambulatory 24-hour pH testing

9. A 62-year-old man has come to discuss management options for his achalasia. He has had symptoms of regurgitation for several years, but has not lost much weight during this time. He has not had pneumonia. A barium swallow study was performed.

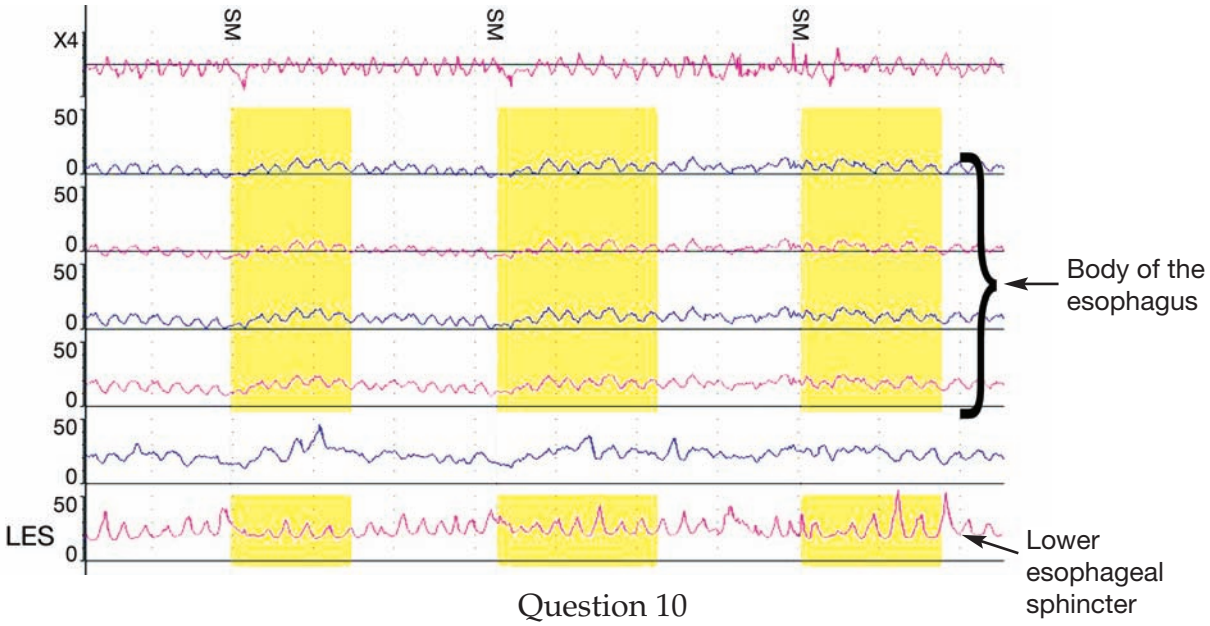


Question 9

The most appropriate therapy for this man would be:

a. Injection of botulinum toxin
b. Pneumatic dilatation
c. Medical therapy with nitrates and calcium channel blockers before meals
d. Diverticulectomy
e. Heller myotomy with diverticulectomy

10. A 32-year-old woman has had heartburn for the last 2 years. She regularly has regurgitation when she bends down. Also, she has dysphagia for liquids and solids. She has had minimal weight loss. The findings of upper endoscopy were unremarkable. An esophageal motility study was performed.



Question 10

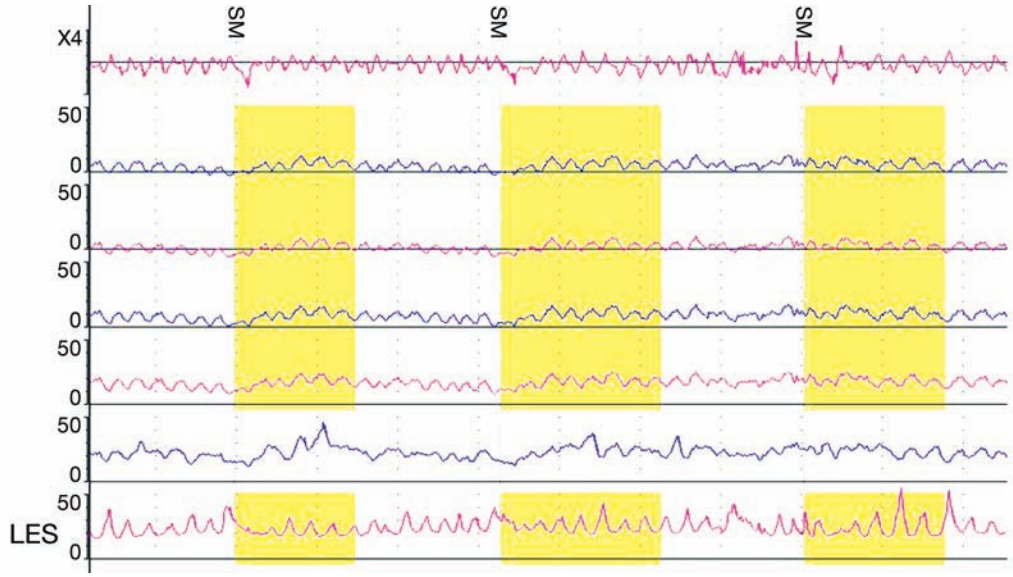
The most appropriate therapy for this woman's condition would be:

a. Injection of botulinum toxin
b. Endoscopic dilatation
c. Medical therapy with double-dose antisecretory therapy and elevation of the head of the bed
d. Heller myotomy
e. Laparoscopic Nissen fundoplication

11. A 23-year-old woman has experienced substernal and epigastric burning sensation as well as postprandial bloating for the past 2 to 3 years. She has not had a response to trials of antacids or H_2 blockers, and she is referred to you for consultation. She has no alarm features such as bleeding or dysphagia. Findings on upper endoscopy are negative. An ambulatory pH study shows 14 episodes of acid reflux, which occurred during 1.2% of the total study time. Of the 14 reflux episodes, 5 were correlated with symptoms of epigastric burning sensation. Treatment with PPIs at the standard dose once daily and then twice daily has not led to any appreciable improvement in her symptoms. What is the appropriate next step?

a. Continue PPI twice daily and repeat endoscopy in 1 year to survey for Barrett's esophagus
b. Refer patient for antireflux surgery
c. Double the dose of PPI
d. Begin a trial with amitriptyline
e. Perform esophageal manometry

12. A 48-year-old man presents with a 4-year history of dysphagia. His symptoms began insidiously but have now progressed to the point that he has trouble swallowing at every meal and has difficulty with liquids as well as solids. He has a sense that food sits in his chest. If he interrupts his meal and waits, the food often passes down into his stomach, particularly after he drinks a large amount of water. However, he has been noticing some nasopharyngeal regurgitation when attempting this maneuver and also notices regurgitation of sour fluid when he bends over. His weight had been stable, but with progressive symptoms over the past 12 months or so, he has now lost approximately 10 lb. Findings on upper endoscopy were unremarkable, including a retroflexed view of the gastroesophageal junction. A manometric recording from the patient is shown below.



Question 12 Manometric recording

What is the diagnosis?

a. Achalasia
b. Nutcracker esophagus
c. Esophageal spasm
d. Severe GERD
e. Scleroderma

13. A 14-year-old boy presents with a 2-day history of chest pain, odynophagia, and dysphagia. He says he does not have any fever, and he has not previously had any swallowing difficulties. EGD shows ulceration and inflammation in the midesophagus without mass. The gastroesophageal junction is normal, and there is no hiatal hernia. What is the most likely diagnosis?

a. *Candida* esophagitis
b. Pill esophagitis
c. Reflux esophagitis
d. Eosinophilic esophagitis

14. A 48-year-old woman presents with a 2-year history of progressive dysphagia. During a recent episode, food got caught in her chest for an hour. She decided to go to the emergency department, but en route, the dysphagia spontaneously resolved and she returned home. She also has a history of progressively severe heartburn over the past 4 to 5 years. Initially, she had a response to once-daily PPI, but therapy became refractory to the treatment. More recently, she has been taking antacids in addition to the PPI, but this affords only partial relief. She has lost approximately 10 lb over the past 6 months because of progressive dysphagia. She states that she does not have any fever, chills, or sweats but has noticed that her fingers often become white or even purple and painful when she is in the cold. EGD shows severe distal esophagitis with a stricture, but no evidence of a mass or Barrett's esophagus. What is the diagnosis?

a. Severe GERD
b. Pill esophagitis
c. Scleroderma
d. Eosinophilic esophagitis

15. The patient presented in question 14 had esophageal manometry that showed normal peristalsis and contractions in the upper esophagus but a significantly decreased amplitude of contractions with suggestion of aperistalsis in the distal esophagus and low LES pressure. What would be the appropriate next step?

a. Injection of botulinium toxin (Botox) into the LES
b. Titrate up the dose of PPI to control symptoms
c. Fundoplication
d. Swallowed fluticasone spray

ANSWERS

1. Answer a

Dysplasia is a histologic proxy for genetic instability. It is difficult to distinguish dysplasia from reactive atypia that is present in response to inflammation. The 2008 American College of Gastroenterology guidelines recommend, even in the absence of erosive esophagitis, that patients with newly diagnosed low-grade dysplasia alter the PPI regimen and undergo repeat endoscopy in 6 months. If a patient is not already taking a PPI, he or she should begin taking one, even if asymptomatic. If the patient is already using a PPI, confirm that he or she is taking it correctly (meaning on an empty stomach, 20-60 minutes before chewing a solid). If the medicine is taken correctly once daily, the patient has a choice of either increasing the dose to twice daily or changing to a different PPI. Repeat endoscopy in 8 to 12 weeks serves two purposes: to ensure healing of the esophagitis and to clarify the degree of dysplasia in the underlying Barrett's segment.

The 6-month repeat endoscopy option reflects the 1998 American College of Gastroenterology guidelines for the management of low-grade dysplasia.

Photodynamic therapy should be offered to patients who have high-grade dysplasia or carcinoma in situ. Because photodynamic therapy has a significant morbidity profile, with 33% of patients experiencing recalcitrant esophageal strictures or skin reactions affecting the quality of life, it is not recommended for patients with a low risk of cancer. Also, in most series, 15% of patients have residual intestinal metaplasia after photodynamic therapy. The effect of laser treatment on these residual clones is not clear.

Although fundoplication may be an excellent option in the near future for this patient, he is better served by ensuring that there is no significant dysplasia underlying the esophagitis. If repeat

endoscopy shows that the esophagitis has healed and there is no significant dysplasia in the Barrett's segment, fundoplication with hiatal hernia repair would be a reasonable option. If the patient instead has high-grade dysplasia or neoplasm, esophagectomy, not fundoplication, would be the optimal operation.

Neither fundoplication nor acid-suppression medications have been shown definitively to diminish the risk of esophageal adenocarcinoma in patients with GERD or Barrett's esophagus.

In response to the patient's query, esophagectomy is the only option that would diminish his risk of esophageal cancer. However, esophagectomy would not be a wise choice because of its inherent high risk of mortality (ranging from 1% at high volume centers up to 20% at centers that perform few operations) and morbidity. Over time, there also is a possibility of recurrent Barrett's esophagus proximal to the esophagogastric anastomosis. The risks of esophagectomy are too great to offer this option to a patient with reactive atypia or low-grade dysplasia in the short Barrett's segment.

2. Answer e

Esophagectomy is the standard of care for patients confirmed to have high-grade dysplasia. The 3-cm area of nodularity is of concern for concomitant neoplasm.

Alteration of the PPI regimen, followed by repeat EGD in 3 months with intensive biopsy sampling is an option permitted by the American College of Gastroenterology. The underlying assumption of this option is that definitive treatment will be recommended when the cancer is demonstrated. The challenge is that locoregional micrometastases or, worse, distant metastases may be present by that time. For patients with significant comorbid conditions that also threaten longevity, this watchful waiting approach is very reasonable. Because the patient is in otherwise excellent health, observation is a less attractive option.

Performing endoscopic mucosal resection for staging purposes is an excellent option, but it is not an excellent choice for treatment in this scenario. Endoscopic mucosal resection is technically easier to perform on lesions 1 cm or smaller in diameter, although a piecemeal approach can be undertaken for larger lesions. Mucosectomy of the region of nodularity might treat the nodule, but it will not address the high-grade dysplasia present at the distal aspect of the Barrett's segment.

The challenge in opting for endoscopic mucosal resection of the nodule, followed by photodynamic therapy of the remaining Barrett's segment, is the risk of micrometastases in regional lymph nodes. For patients with superficial tumors, this risk is approximately 7%.

Photodynamic therapy alone does not treat the nodule.

3. Answer b

The standard of care for early potentially curable esophageal adenocarcinoma is esophagectomy. Regional lymph nodes are resected en bloc with this maneuver, which is the major advantage over mucosal resection with superficial ablation therapy. If the patient is able to tolerate surgery, esophagectomy should be offered. Endoscopic mucosal resection with photodynamic therapy is best for patients with a nodule of high-grade dysplasia or cancer of T1 extent.

In a recent survey of gastroenterologists, medical oncologists, radiation oncologists, and thoracic surgeons, the patient group for whom all subspecialists were in agreement about treatment were those with early-stage disease. Consistently, esophagectomy was recommended by all subspecialists. Definitive chemoradiation therapy and endoscopic mucosal resection, followed by photodynamic therapy, usually are offered to patients who are not surgical candidates or to those who decline esophagectomy. Neoadjuvant chemoradiation therapy usually is recommended to patients without distant metastases in whom spread to regional lymph nodes has been demonstrated. Adjuvant chemoradiation therapy usually is recommended for patients who had surgery and for whom the preoperative impression was early-stage disease but postoperative examination of the specimen shows micrometastases to regional lymph nodes.

4. Answer d

The differential diagnosis for this African American woman includes nonerosive reflux disease, pill esophagitis, and reflux esophagitis. Because of her

comorbid conditions, some of which may be treated with immunosuppressive medications, infection with *Candida* or a virus (cytomegalovirus or herpes), is also part of the differential diagnosis. In view of her race and sex, neoplasm and Barrett's esophagus are highly unlikely. Barrett's esophagus is an uncommon disorder (3.5%-7% of symptomatic adults who undergo endoscopy). The prevalence of Barrett's esophagus is 3- to 4-fold less in females than in males and least common among African American females.

An upper gastrointestinal barium study usually is helpful in evaluating dysphagia, in searching for fine rings or webs, or in helping to distinguish achalasia from scleroderma in patients with esophageal aperistalsis. Because the patient does not have dysphagia, an upper gastrointestinal barium study would likely have low yield.

Although a capsule study to screen for Barrett's esophagus and reflux esophagitis is reasonable, its ability to screen for viral disorders or pill esophagitis has not been documented.

Diagnosing Barrett's esophagus is presumed to be beneficial for patients in whom dysplasia or an early curable esophageal neoplasm is found (T1 or T2N0M0), because steps can be taken to eradicate the disease. With this patient's general poor health status (New York Heart Association class IV heart failure), she is not an optimal surgical candidate. Were endoscopy performed and Barrett's esophagus diagnosed, long-term surveillance would not be recommended. Even for persons with excellent general health, surveillance of Barrett's esophagus has not been proven to save lives. Despite this fact, largely due to biologic plausibility, surveillance is recommended for persons healthy enough to tolerate an intervention (such as esophagectomy or photodynamic therapy) if high-grade dysplasia or carcinoma in situ is found. The recent availability of new therapeutic options, including endoscopic mucosal resection with photodynamic therapy and balloon-based circumferential endoscopic radiofrequency ablation, is making the decision for whom to end surveillance more difficult.

It is premature to recommend fundoplication for this patient because the diagnosis is not yet clear and the patient is not a good surgical candidate.

Empiric treatment with a PPI, changing the medications to liquid form, and encourageing her to drink a glass of water with the pills and then remaining upright for 1 hour are reasonable initial recommendations.

5. Answer e

It is not clear if this patient has Barrett's esophagus or intestinal metaplasia of the cardia, which is thought to be a normal variant. Intestinal metaplasia of the cardia is common. It occurs equally in males and females, despite the presence or absence of GERD symptoms. Regardless of the indication for endoscopy, biopsy specimens from the end of the tubular esophagus show intestinal metaplasia with goblet cells (so-called Barrett's cells) in the distal esophagus of 15% to 20% of US adults. Patients with Barrett's esophagus, in whom the endoscopist observes abnormal salmon-colored mucosa in the tubular esophagus and the pathologist confirms specialized intestinal mucosa, have a 30- to 125-fold increased risk of adenocarcinoma. Although no prospective study has shown prolongation of life expectancy with surveillance, professional gastrointestinal societies have recommended surveillance for patients with Barrett's esophagus. Because persons with intestinal metaplasia with goblet cells at the cardia have the same risk of esophageal adenocarcinoma as the general population, about 3 to 4 per 100,000 persons per year, surveillance has not been recommended by any gastrointestinal society. One multi-international expert consensus panel has written guidelines that oppose the collection of biopsy specimens from the normally located, normal-appearing zig-zag line (squamocolumnar junction) because of the fear and anxiety it generates in patients and the negative societal outcomes, including an increase in insurance premiums, associated with the diagnosis of Barrett's esophagus.

On the basis of the endoscopic description, it is unclear whether this patient has Barrett's esophagus or intestinal metaplasia of the cardia. Therefore, it probably is wise to assume that the patient may have Barrett's esophagus and, hence, reasonable to schedule confirming/surveillance endoscopy 1 year after the initial endoscopic examination. Because the first endoscopic examination

did not show dysplasia or overlying erosive esophagitis, the examination does not need to be repeated any sooner than 1 year.

Treatment with a PPI, generic or otherwise, is not recommended because the patient is asymptomatic and no dysplasia was detected. Similarly, fundoplication is not recommended because the patient is asymptomatic.

6. Answer c

The definition of achalasia requires aperistalsis throughout the smooth muscle part of the esophagus, often with increased LES pressure. A patient with scleroderma would present with very low-amplitude esophageal waves and occasionally with aperistalsis, although the LES tone would be very low. Nutcracker esophagus is a phenomenon that has been described as high-amplitude waves that are peristaltic. According to the definition of diffuse spasm, more than 30% of the wet swallows are simultaneous but occasional peristalsis is present.

7. Answer b

The radiograph clearly shows findings typical of achalasia, that is, a dilated esophagus that tapers, producing a "bird's beak" appearance. With diffuse spasm, the radiograph would show a more corkscrew appearance. With scleroderma, the radiograph may be normal, with a widely patent LES. Nutcracker esophagus is a manometric finding, with the mean distal esophageal amplitude more than 180 mm Hg. Peristalsis is maintained and, in most cases, the esophagogram is normal.

8. Answer b

The tongue fasciculations suggest motor neuron disease and bulbar palsy, in which oropharyngeal dysphagia frequently occurs. Oropharyngeal dysphagia is evaluated with real-time videofluoroscopy. EGD is not helpful in evaluating this form of dysphagia; it would be more appropriate in differentiating causes of esophageal dysphagia. Furthermore, standard esophageal manometry has very limited application in evaluating the oropharynx. Ambulatory 24-hour pH studies would be useful to evaluate for acid reflux and regurgitation, but this patient does not have any of these symptoms.

9. Answer e

The barium swallow study shows evidence of a distal esophageal diverticulum and a dilated esophagus. This is seen in achalasia, with a diverticulum forming in response to a hypertensive LES. The treatment of choice would include diverticulectomy and myotomy. Diverticulectomy alone would not solve the problem of the increased LES pressure causing the diverticulum. No medical therapy is effective for distal esophageal diverticula or achalasia. Injection of botulinum toxin would not be effective in treating a well-established symptomatic diverticulum, and pneumatic dilation would not have an effect on the diverticulum. It would treat only the LES, and, this patient may have a higher risk of perforation.

10. Answer d

The tracing shows an aperistaltic esophagus with an LES that has normal tone but does not relax. Often, the LES is hypertensive, but in up to one-third of cases, it may appear to be in the normal range. This is typical of achalasia, and for a young person, the treatment would be laparoscopic Heller myotomy. Endoscopic dilation with the pneumatic balloon technique is a possibility; however, given the patient's age, surgery would be preferable because it is more durable. In addition, up to 30% of patients with achalasia complain of heartburn symptoms that are thought to be caused by fermentation. However, antireflux surgery would make the problem worse by further obstructing the esophagus (increased LES pressure). Although PPI therapy may be prescribed, it does not treat the underlying condition. Injection of botulinum toxin in a young person with achalasia is not recommended because its durability is limited.

11. Answer d

This patient has symptoms of dyspepsia and substernal burning sensation. She has not had a response to PPI therapy, and the ambulatory pH value is not consistent with significant GERD. Therefore, surveillance is not needed for Barrett's esophagus, and there is no reason to expect fundoplication to improve these functional symptoms. In fact, functional symptoms often worsen after fundoplication. Similarly, there is no reason to expect improvement

after doubling the dose of PPIs. Because she has no dysphagia, manometry is not indicated. As for other functional problems, functional heartburn may respond to tricyclic antidepressants, and a trial of amitriptyline would be indicated.

12. Answer a
This man's history is consistent with an esophageal dysmotility. Manometry shows aperistalsis in the body of the esophagus, increased resting LES pressures, and incomplete relaxation of the LES. This history and these manometric findings are classic for achalasia. The manometric features are not consistent with any of the other options.

13. Answer b
Midesophageal ulcers without associated mass or stricture is suggestive of pill esophagitis. The acute onset of these symptoms with odynophagia would be unusual for GERD; furthermore, his gastroesophageal junction is normal. Midesophageal ulceration is not a typical finding for *Candida* esophagitis, and in this otherwise healthy young man that diagnosis would be unusual. Eosinophilic esophagitis is an increasingly appreciated cause of esophageal symptoms, particularly in young men. However, findings of midesophageal ulcers and acute onset of symptoms would be unusual for this diagnosis. This young man had recently started taking tetracycline for severe acne. His symptoms resolved with PPI therapy and discontinuation of tetracycline therapy.

14. Answer c
This patient has had progressively severe heartburn and progressive dysphagia. The response to PPI therapy has been lost, and she is now losing weight. Her age and severe esophagitis make the diagnosis of eosinophilic esophagitis unlikely. The constellation of progressively severe heartburn and dysphagia with Raynaud's phenomenon and telangiectasias makes scleroderma the most likely diagnosis.

15. Answer b
Manometry confirms the clinical suspicion of scleroderma. Injection of botulinium toxin into the LES may afford temporary relief for achalasia but would not be expected to have a benefit and perhaps would even cause worsening of this patient's condition; she already has low LES pressure. With the progressive dysphagia and poor motor function in the distal esophagus, fundoplication may well worsen swallowing function. This option might be considered if titration of the PPI dose fails. The history and findings are not consistent with eosinophilic esophagitis, and there is no reason to try swallowed fluticasone spray.

Section II

Stomach

Peptic Ulcer Disease

Dawn L. Francis, MD, MHS

A peptic ulcer is a break in the gastric or duodenal mucosa that penetrates down to the muscularis mucosae (Fig. 1). The presence of such an ulcer constitutes the diagnosis of *peptic ulcer disease* (PUD). PUD is common and is a major source of morbidity and health care expenditure in the United States, affecting 200,000 to 400,000 people annually and accounting for as much as 10% of medical costs for digestive diseases.

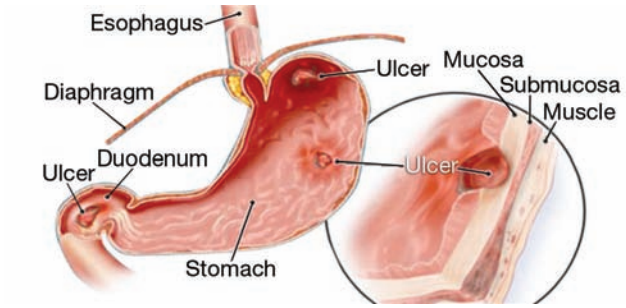


Fig. 1. Diagram of a peptic ulcer. (From MedicineNet [Internet]. Peptic ulcer disease. San Clemente, CA: MedicineNet Inc.; c1996-2008. [cited 2008 May 19]; [about 6 screens]. Available from: http://www.medicinenet.com/peptic_ulcer/article.htm. Used with permission.)

EPIDEMIOLOGY

The incidence of patients with diagnosed PUD ranges from 0.1% to 0.3% per year. Peptic ulcers become more common with increasing age, and traditionally, they have been more common in men than in women. Persons infected with *Helicobacter pylori* have nearly a tenfold increase in incidence at 1% per year. The incidence increases with age for both duodenal and gastric ulcers. The lifetime prevalence of clinically evident PUD in the United States is approximately 10% for the general population and 20% for patients infected with *H. pylori*.

Several trends are notable in the prevalence of PUD in the United States: the prevalence has been decreasing during the past several decades; the disease now affects males and females at increasingly similar rates (previously, males were affected more often), and the frequency of gastrointestinal tract hemorrhage due to PUD is decreasing in younger persons but increasing in the elderly.

PATHOPHYSIOLOGY

The acid environment of the stomach and the frequency with which noxious agents are ingested

Abbreviations: CLO, Campylobacter*-like organism; COX, cyclooxygenase; EGD, esophagogastroduodenoscopy; NSAID, nonsteroidal antiinflammatory drug; PUD, peptic ulcer disease.*

create a fertile ground for the development of ulcers. Indeed, in view of these continuing insults, PUD is surprisingly uncommon, a fact that underscores the importance of the protective mechanisms of the gastric mucosa.

Peptic ulcers are the result of an imbalance between mucosal insults and mucosal defense mechanisms. Several protective mechanisms can keep peptic ulcers from developing in the healthy state. These include the surface mucus and bicarbonate layer, the epithelial barrier, tight intercellular junctions, mucosal blood flow-mediated removal of back-diffused acid, and cell restitution and epithelial renewal (Fig. 2). When these mechanisms are interrupted or are nonfunctioning, the mucosa is vulnerable to various insults. This is likely why certain disease states, such as shock or cardiovascular disease, liver disease, or renal failure, are predisposing conditions for the development of PUD.

Most ulcers, however, occur when the normal mechanisms are disrupted by superimposed mucosal insults that overwhelm the protective mechanisms of the upper gastrointestinal tract. The most common insults are the result of *H. pylori* infection and use of nonsteroidal antiiflammatory drugs (NSAIDs). Uncommon causes include gastric acid hypersecretion (as in Zollinger-Ellison syndrome),

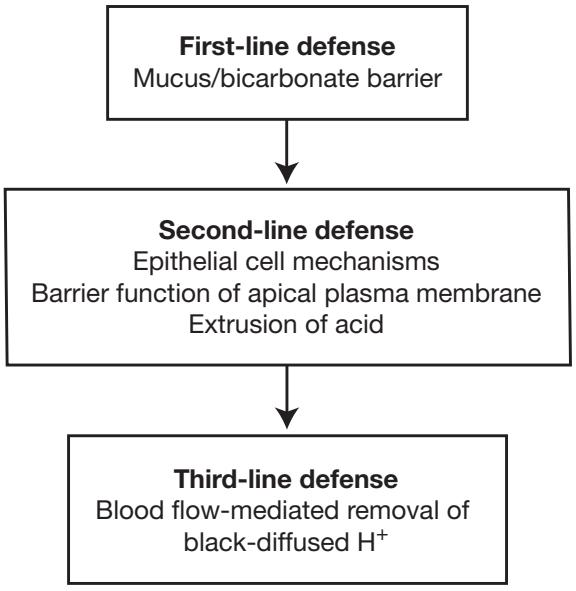


Fig. 2. Mucosal defense mechanisms.

antral G-cell hyperplasia, and mastocytosis. Viral infections with herpes simplex virus and cytomegalovirus, inflammatory disorders such as Crohn's disease or sarcoidosis, and radiation injury can all cause ulceration in the gastrointestinal tract, including the stomach and duodenum.

Helicobacter pylori

H. pylori infection is the major cause of PUD worldwide. The infection rate for patients with PUD ranges from region to region: in high prevalence regions, such as Southern Europe and Japan, the rate is more than 90%, whereas in low prevalence regions, such as Northern Europe and the United States, it is 50% to 75%.

Throughout the world, the infection is acquired typically in childhood. The specific mode of transmission has not been defined fully, but there is evidence that the organism is transmitted from person to person. It likely is transmitted by oral-oral or fecal-oral routes.

In the developing world, the majority of children are infected with *H. pylori* before the age of 10 years and more than 80% of adults are infected by the age of 50 years. In the United States, serologic evidence of *H. pylori* infection is uncommon before age 10 years and is found in about 60% of the population by the age of 60 years.

There is broad evidence to support a pathogenic role of *H. pylori* in PUD. Most notably, patients with PUD have a much higher rate of infection with *H. pylori* than the general population; antibiotic therapy heals ulcers at the same rate as H_2-receptor antagonists; the recurrence rate of peptic ulcers is lower after *H. pylori* infection has been eradicated than after conventional ulcer treatment, and ulcer recurrence usually is associated with failure to eradicate the infection.

The Organism

H. pylori is a gram-negative helical-shaped bacterium that has four to six flagella. These bacteria colonize only gastric epithelium. When they are found elsewhere in the gastrointestinal tract (eg, the gastroesophageal junction or duodenum), they are associated with metaplastic gastric epithelium.

To survive the hostile environment of the stomach, *H. pylori* produce urease that generates ammonia, which, in turn, neutralizes acid. These

organisms also produce a protease that allows them to move through the mucous layer. However, this protease thins the mucous layer and is responsible for damaging this first barrier of mucosal defense.

H. pylori infection causes a chronic active gastritis that involves predominantly the gastric antrum. The presence of these bacteria in the antrum leads to a loss of D cells that release somatostatin, and this allows the uninhibited release of gastrin by antral G cells. This leads to increased gastric acid secretion that promotes and sustains ulcer formation. *H. pylori* infection also incites the development of duodenitis and gastric metaplasia of the duodenum, which may contribute to the development of duodenal ulceration.

The critical role of *H. pylori* in the development of PUD is clear. What is not clear is why so few patients with *H. pylori* infection develop clinical ulcerations. Host immune responses, genetic predisposition, bacterial virulence factors, and other environmental factors have been implicated, but none has been established clearly as the single factor responsible for the development of PUD.

Nonsteroidal Antiinflammatory Drugs

PUD that is not due to *H. pylori* infection usually is due to the use of NSAIDs. Many patients do not report using these drugs, so for any patient with PUD, clinicians must maintain a high degree of suspicion. In the United States, up to 17 million people take NSAIDs daily. Of these, 200,000 will have serious side effects (including gastrointestinal tract bleeding) and approximately 6,000 will die. Up to 3% of all NSAID users will develop serious gastrointestinal complications (symptomatic PUD, bleeding, or perforation), and 20% will develop asymptomatic PUD or gastropathy within the first year of use.

NSAIDs disrupt the gastrointestinal tract mucosal defense mechanisms by topical and systemic effects. Topical damage can occur within the stomach by direct injury to the gastric epithelium. Systemically, the inhibition of prostaglandins disrupts mucosal blood flow, alters mucus secretion, and inhibits bicarbonate secretion, all of which may lead to increased hydrogen ion back diffusion and mucosal injury. Also, the inhibition of prostaglandins may lead to a break in the tight intercellular junctions and to trapping of neutrophils within the capillaries. These neutrophils release cytokines and increase the inflammatory reaction.

The American College of Gastroenterology has reviewed the data regarding the risk factors for NSAID toxicity and has listed the five most important characteristics that place patients at risk for NSAID-related gastrointestinal complications: previous history of a gastrointestinal event (ulcer or hemorrhage), age older than 60 years, high dosage of NSAIDs, concurrent use of glucocorticoids, and concurrent use of anticoagulants. Assessment of these risk factors is appropriate to identify patients who should be considered for prophylaxis if it is thought that NSAID therapy is required.

Specific Agents

Low-dose Aspirin

Aspirin has been in use for more than a century as an analgesic and in use for the past several decades for the prevention and treatment of cardiovascular disease and stroke. With widespread usage, its association with gastrointestinal complications, including PUD and hemorrhage, has become clear. The effects of aspirin on the gastrointestinal tract likely are due to the mechanisms mentioned above, but they also may be due to the antiplatelet aggregation mechanism of aspirin. Therefore, not only is there a higher likelihood of mucosal injury, but the result of the insult (ie, PUD) is more likely to be associated with hemorrhage. The effects of aspirin on the gastrointestinal tract are dose dependent in the dosage range of 75 to 300 mg daily, which may cause a twofold to threefold increase in the risk of gastrointestinal tract bleeding due mostly to upper gastrointestinal tract ulceration but also to injury to the lower gastrointestinal tract.

Cyclooxygenase-2 Inhibitors

Cyclooxygenase (COX)-2 inhibitors have been promoted as selective NSAIDs with less risk of gastrointestinal complications than nonselective NSAIDs. Controlled trials with COX-2 inhibitors have shown a decreased risk of clinically apparent peptic ulcers and their complications, although the incidence of PUD among those taking these drugs appears to be as high as 5%. In addition, low-

dose aspirin has a synergistic effect with COX-2 inhibitors; thus, patients who take both drugs are at greater risk for gastrointestinal complications than if they take either drug alone.

There is no evidence that COX-2 inhibitors have advantages over other NSAIDs for patients with unhealed ulcers. Also, COX-2 inhibitors appear to inhibit the healing of peptic ulcers. Over the past several years, many drugs from this class have been removed from the US market because of an apparent increase in risk of stroke and cardiovascular disease.

Helicobacter pylori and Nonsteroidal Antiinflammatory Drugs

The relationship between *H. pylori* and NSAIDs is complex. *H. pylori* infection appears to be a significant risk factor for PUD in NSAID-naïve patients who begin NSAID therapy. Several randomized controlled trials have shown that patients in whom *H. pylori* infection is eradicated before they are treated with NSAIDs have a much lower rate of PUD. In addition, a meta-analysis of observational studies found evidence of synergism between *H. pylori* infection and NSAIDs in both PUD and ulcer with hemorrhage.

The available data support testing for and treating *H. pylori* infection before the initiation of long-term NSAID therapy. If patients with PUD have *H. pylori* infection and must continue receiving NSAID therapy, the infection should be treated and consideration should be given to providing the patient with a prophylactic acid-suppressive regimen (ie, a proton pump inhibitor) to reduce the risk of additional ulcers and associated complications.

Gastric Acid

The presence of gastric acid is the reason the upper gastrointestinal tract is especially prone to the development of ulceration. The long-held dictum "no acid, no ulcer" still applies. Once there is a mucosal break, whether due to failure of the inherent protective mechanisms or overwhelming mucosal injury, the break is maintained and propagated by the presence of gastric acid.

Gastric acid is produced by parietal cells. Parietal cells have receptors for three stimulants: histamine, acetylcholine, and gastrin (Fig. 3). Histamine is manufactured by enterochromaffin-like cells and mast cells. Acetylcholine is released by the vagus nerve. Gastrin is produced and released by the antral G cells. G cells are inhibited by gastric acid, creating an important negative feedback mechanism to protect against the hypersecretion of gastric acid.

The two major inhibitors of acid production by parietal cells are prostaglandins and somatostatin. Prostaglandins are released by both epithelial and nonepithelial cells in the stomach, and somatostatin is released by D cells in the stomach.

Most patients with gastric ulcers do not have an increased amount of gastric acid. In fact, most have normal or low-normal amounts of gastric acid (perhaps because *H. pylori* infection can decrease the production of gastric acid). This is also true for most patients who have duodenal ulcers, but there is a small subset of patients with duodenal ulcers who are gastric acid hypersecretors (see below).

Hypersecretion of Gastric Acid

The risk of developing PUD is augmented by hypersecretion of gastric acid. Acid hypersecretory states are often complicated by multiple ulcerations in unusual locations. Because the mechanism of injury is damage from gastric acid, the stomach typically is not involved. More commonly, ulcerations occur in the duodenum and esophagus.

The increased production of gastric acid disrupts normal digestion and absorption. Many

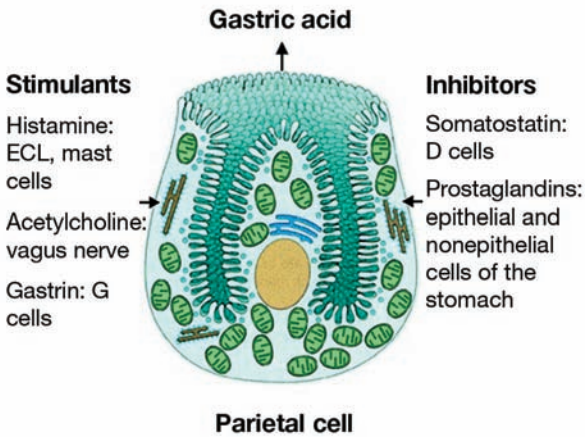


Fig. 3. Physiology of the parietal cell. ECL, enterochromaffin-like.

digestive enzymes require an alkaline environment to be active, and ulcer disease itself can limit directly the absorption of nutrients because of disruption of the intestinal villi. As a result, disease states associated with gastric acid hypersecretion can be associated with diarrhea, malabsorption, and weight loss. These disease states include Zollinger-Ellison syndrome, systemic mastocytosis, antral G-cell hyperplasia, and retained antrum syndrome.

Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome is characterized by PUD, gastric acid hypersecretion, and a gastrin-producing tumor (gastrinoma). Gastrinomas are rare and occur in fewer than 1% of patients who have PUD. If surgical resection of the gastrinoma is not possible, then the main objective of treatment is suppression of gastric acid production. This typically requires administration of a proton pump inhibitor twice daily.

Systemic Mastocytosis

Systemic mastocytosis is characterized by multiorgan mast cell infiltration, including infiltration of the skin, gastrointestinal tract, lymph nodes, bone marrow, and liver. Hypersecretion of acid, produced by increased histamine levels, is found in approximately 30% of patients. Because the hypersecretion of acid in this condition is due to histamine stimulation of parietal cells, H_2-receptor antagonists are effective therapy.

Antral G-cell Hyperplasia

Antral G-cell hyperplasia is a rare condition described in a cluster of patients with an extensive family history of PUD and an increased number of antral G cells. These patients have hypergastrinemia and, as a result, gastric acid hypersecretion. A secretin stimulation test can distinguish between antral G-cell hyperplasia and Zollinger-Ellison syndrome. Rather than the marked increase in gastrin in response to secretin stimulation seen in Zollinger-Ellison syndrome, the response in antral G-cell hyperplasia is a decrease, no change, or a slight increase in the serum level of gastrin (<200 pg/mL). Once antral G-cell hyperplasia is diagnosed, aggressive acid suppression is often effective for healing and preventing ulcers.

Retained Antrum Syndrome

Retained antrum syndrome is a rare form of hypergastrinemia in patients who have had a Billroth II operation (Fig. 4). If a small cuff of antrum remains in the afferent limb and is excluded from exposure to gastric acid, the gastrin-producing G cells will release gastrin without control by the negative feedback loop, leading to hypersecretion of acid in the remaining stump.

Viral Causes of Upper Gastrointestinal Tract Ulceration

Viruses can cause ulceration of the upper gastrointestinal tract in any patient, but this is more common in patients with immunodeficiency. The most common causes for immunodeficiency associated with viral infection of the gastrointestinal tract are immunosuppression related to solid-organ or bone marrow transplantation, human immunodeficiency virus infection associated with acquired immunodeficiency syndrome, and treatment of autoimmune or inflammatory diseases (including treatment of inflammatory bowel diseases with biologic agents). The viruses commonly associated with ulceration of the upper gastrointestinal tract are herpes simplex virus and cytomegalovirus. Viral infection should be strongly suspected in patients who are immunosuppressed and develop PUD. In such cases,

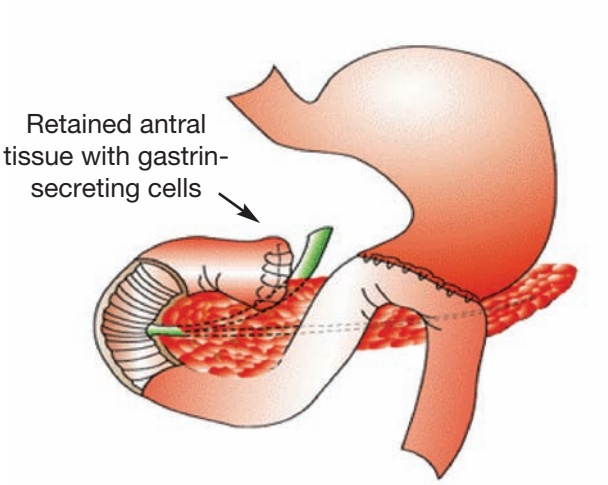


Fig. 4. Retained antrum after Billroth II operation. (Modified from Costamagna G. ERCP after Billroth II reconstruction [Internet]. UpToDate c2008 [cited 2008 May 9]. Available from: http://www.uptodate.com/. Used with permission.)

biopsy specimens should be obtained from the ulcer margin (where herpes simplex virus commonly resides) and the ulcer base (where cytomegalovirus is found). If an upper gastrointestinal tract ulceration has a viral cause, it is important that it be diagnosed because the management is completely different from that of PUD due to other causes.

Radiation

The second portion of the duodenum is especially sensitive to radiation injury after abdominal radiation. These ulcers usually can be treated with aggressive acid suppression. In rare cases, surgical resection of large nonhealing ulcers has been necessary.

Sarcoidosis

When sarcoidosis involves the gastrointestinal tract, it usually affects the stomach. Ulceration can occur that resembles PUD. Other endoscopic findings may be nodular gastritis, thickened mucosal folds, polypoid lesions, or deformities in the gastric body or antrum. Acid suppression may be helpful in patients with PUD due to sarcoidosis. Systemic treatment with corticosteroids or NSAIDs may be hazardous in patients with a sarcoid-induced ulcer. Surgery is often required in patients with pyloric stenosis or gastrointestinal tract bleeding.

Additional Risk Factors

Smoking

Smoking has an important facilitative role for PUD. Studies performed before the discovery of *H. pylori* showed that smokers were more likely to develop ulcers, and the ulcers were more difficult to treat and more likely to recur. There are several potential mechanisms by which smoking can foster PUD. The most likely are compromised blood flow to the mucosa and nicotine stimulation of basal acid output.

Alcohol

Alcohol can damage the gastric mucosal barrier directly and cause acute gastric mucosal lesions characterized by mucosal hemorrhages. Alcohol also stimulates acid secretion. However, despite the acute effects of alcohol on the gastric mucosa, there is no clear evidence that alcohol causes or exacerbates chronic PUD. When alcohol use is associated with chronic liver disease, the liver disease itself can increase the risk of PUD, likely because of altered mucosal blood flow.

Other Drugs

Corticosteroids

Current evidence supports a role of corticosteroids in increasing the risk of PUD, but only when coadministered with NSAIDs.

Platelet-active Agents

Antiplatelet agents have been associated with a high risk of gastrointestinal tract bleeding, especially when administered to patients with previous gastrointestinal tract bleeding. These agents are contraindicated for high-risk patients when administered alone or in combination with NSAIDs.

Sirolimus

Sirolimus has been associated with aggressive ulcer disease in patients undergoing transplantation. Use of this agent in patients with a history of PUD should be approached with caution. Also, PUD that develops while a patient is receiving sirolimus therapy should be treated aggressively.

Bisphosphonates

The association of bisphosphonates with PUD is a matter of controversy and has been studied primarily with the agent alendronate. Acute ulceration has been observed, but the frequency with which ulceration develops into a clinically significant problem is undefined. It is known that the risk of PUD is increased markedly with the concomitant use of NSAIDs and bisphosphonates.

Diet

For centuries, dietary indiscretion has been implicated as a cause of ulcers. Although it is well understood that particular foods, beverages, and spices can cause dyspepsia, there is no evidence that foods cause or promote PUD or interfere with ulcer healing. In the past, dietary modifications had been advised for PUD to enhance healing. These included frequent feedings, bland diets, or dairy-based diets. These interventions do not appear to affect the outcome of PUD.

Psychologic Factors

After decades of study, the importance of psychologic factors in PUD is still debated. Psychologic stressors, depression, and anxiety have been shown to impair endoscopically documented healing and to promote recurrence of endoscopically diagnosed ulcers. Furthermore, the effects of stress seem to be reversible in that PUD which develops after traumatic life events tends to heal after the stress has resolved. The mechanisms that underlie stress and PUD have not been clarified. Any observation of a relationship between psychologic stressors and PUD does not establish causality. For example, a study has found that anxiety and neuroticism were high in a group of patients at the time of diagnosis of duodenal ulcer, but these psychologic symptoms had normalized in patients free of PUD at the end of 10 years of follow-up. This finding questions whether psychologic features are the result, rather than the cause, of PUD.

CLINICAL FEATURES

The clinical features of PUD range from silent ulceration to dyspepsia and epigastric pain. The classic clinical feature of PUD is pain that occurs 2 to 3 hours after a meal, improves with food or antacids, and awakens the patient several hours after the patient falls asleep. *Complicated PUD* implies that the patient has suffered systemically from PUD, for example, with gastrointestinal tract hemorrhage or perforation.

The diagnosis of PUD usually is based on the results of an upper gastrointestinal tract radiographic study or esophagogastroduodenoscopy (EGD). The findings of these two tests correlate in about 80% to 90% of cases. EGD is the preferred method for evaluating PUD because it allows for biopsy of the antrum for *H. pylori* and for biopsy of gastric ulcers to differentiate benign from malignant ulcers.

Diagnosis of *Helicobacter pylori* Infection

The evaluation and treatment of *H. pylori* infection are important aspects of the management of PUD. However, testing for *H. pylori* can be difficult. Part of the difficulty is that false-negative studies for *H. pylori* infection are common. Some of the most common tests for *H. pylori* infection depend on the number of organisms (breath and stool antigen tests, urease testing, histology, and culture), and the number of organisms is influenced by treatment with bismuth, proton pump inhibitors, and antibiotics. If these drugs are being taken by the patient, then *H. pylori* testing should be repeated after the patient has stopped taking them for a sufficient time (typically 4-6 weeks). Because of the high prevalence of *H. pylori* infection among patients with known ulcers and the commonality of false-negative *H. pylori* infection diagnostic tests, negative tests should be confirmed by a second, independent test for patients with PUD.

Several different tests can be chosen to evaluate for the presence of *H. pylori* (Table 1). These can be grouped into two categories: invasive and noninvasive tests. The noninvasive tests are *H. pylori* serology, *H. pylori* stool antigen assay, and the urease breath test. Invasive tests include histopathology, the *Campylobacter*-like organism (CLO) test, and culture.

Noninvasive Tests

Serology

The choice of test depends on the question being asked. For patients who have PUD and have not been treated previously for *H. pylori* infection, serologic testing for evidence of current or previous infection may be appropriate. This test is inexpensive and noninvasive, and it is as sensitive and specific as biopsy for the initial diagnosis of *H. pylori* infection. However, serologic testing does have limitations: it only provides evidence of the patient being infected at some point with *H. pylori* but does not provide information about current infection. Also, as many as 10% of patients who have been infected with *H. pylori* may have a negative test result because of immunoglobulin deficiency. This problem is more common in the elderly.

Stool Antigen

The *H. pylori* stool antigen assay appears to be highly accurate. It is noninvasive, simple, and cost-effective. Its advantage over serologic testing is that it evaluates active infection; thus, it can be used both as an initial test and as a test to evaluate for eradication. As with any test that is reliant on bacterial load, the stool antigen assay can be falsely negative in patients who recently received treatment

Table 1. Diagnostic Tests for *Helicobacter pylori*

Test	Sensitivity, %	Specificity, %	Cost, $
Nonendoscopic tests			
In-office antibody test	88-94	74-88	10-30
ELISA on serum	86-94	78-95	40-100
Stool antigen test	94	92	180
Urease breath test	90-96	88-98	250-300 ($_{13}$C) 20-65 ($_{14}$C)
Endoscopic tests			
Biopsy urease test	88-95	95-100	6-20
Histology	93-96	98-99	60-250
Culture	80-98	100	150

ELISA, enzyme-linked immunosorbent assay.

with antibiotics, bismuth, or proton pump inhibitors. For this reason, the test should be administered 4 to 6 weeks after the completion of treatment for *H. pylori* infection.

Urease Breath Test

If urease, produced by *H. pylori*, is present in the stomach, labeled carbon dioxide is split off and absorbed and easily measured in expired breath. This test is accurate, but it also depends on bacterial load, making it prone to false-negative results in patients who recently received antibiotic or proton pump inhibitors. This traditionally had been the test used to confirm the eradication of infection, but it should be performed 4 to 6 weeks after therapy has been completed.

Invasive Tests

Histology

Biopsy with histologic examination is considered the "gold standard" for the diagnosis of active *H. pylori* infection. It has been recommended that two biopsy specimens be taken from the gastric antrum, two from the gastric fundus, and one from the incisura to yield the greatest sensitivity. If the number of bacteria is small, a silver stain may be necessary (Warthin-Starry staining with hematoxylin-eosin is excellent for detecting infection). In addition to the diagnosis of *H. pylori* infection, histologic examination of the gastric tissue may also identify changes in the gastric mucosa caused by the *H. pylori* infection, such as intestinal metaplasia or dysplasia. The disadvantage of histology is that it requires endoscopy and is more expensive than the noninvasive tests described.

Campylobacter-*like Organism Test*

Mucosal biopsy specimens can be tested for urease with the urease test, the *CLO test*. Like the urease breath test, this test relies on bacterial load and can be affected (ie, increased rate of false-negative tests) by recent gastrointestinal tract hemorrhage. The advantage of the CLO test is that it can be used to evaluate active infection in patients undergoing endoscopy, and it is less expensive than histology. The disadvantages are that it requires endoscopy to obtain the tissue and, in contrast to histologic assessment, it does not allow for the detection of other changes in the gastric mucosa caused by *H. pylori* infection.

TREATMENT

The treatment of PUD has changed remarkably since *H. pylori* infection has been identified and associated with PUD. The recurrence rate of PUD has decreased from up to 95% at 1 year to less than 10% after *H. pylori* eradication. For this reason, it is important initially to consider *H. pylori* infection as a potential cause of ulcer disease in all patients. If the test results are negative, alternative

explanations, such as NSAIDs or hypersecretion of gastric acid, should be considered and evaluated.

Treatment of *Helicobacter pylori* Infection

Treatment regimens for *H. pylori* infection have evolved over the past decade from monotherapy to combinations of antisecretory and antibiotic therapy. A 10- to 14-day course of therapy with bismuth and antibiotics or with a proton pump inhibitor and antibiotics is as effective for inducing ulcer healing as a 4-week course of proton pump inhibitor therapy. Combination therapy enhances the cure of *H. pylori* infection, shortens the treatment period, and has a 90% cure rate at 1 week. The different treatment regimens for *H. pylori* infection are given in Table 2.

H. pylori are innately resistant to several antibiotics (eg, vancomycin, sulfonamides, and trimethoprim). In addition, primary resistance can occur to antibiotics used in several eradication regimens. Both metronidazole- and clarithromycin-resistant strains of *H. pylori* have been reported. The addition of a proton pump inhibitor or bismuth to a metronidazole-based therapy lessens the effect of metronidazole resistance. Metronidazole resistance appears to be a relative phenomenon that can be diminished with a higher dose of metronidazole (500 mg).

Clarithromycin resistance, however, is a problem that cannot be overcome by increasing the macrolide dose. No clarithromycin-based treatment has been shown to treat reliably clarithromycin-resistant organisms. Therefore, if a clarithromycin-based regimen fails to eradicate *H. pylori* infection, a metronidazole-based regimen should be instituted. Resistance has not been found to amoxicillin, tetracycline, or bismuth.

Currently, routine culture for *H. pylori* is not recommended, but patients with refractory disease may be well-served by culture and sensitivity testing because the incidence of resistance is very high in this subgroup.

Table 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) plus clarithromycin 500 mg twice daily, and amoxicillin 1,000 mg twice daily for 10-14 days	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, metronidazole 500 mg twice daily for 10-14 days	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, ranitidine 150 mg orally twice daily (or standard dose PPI once to twice daily) for 10-14 days	75-90

PPI, proton pump inhibitor.

Modified from Chey WD, Wong BCY. American College of Gastroenterology Guideline on the management of Helicobacter pylori *infection. Am J Gastroenterol. 2007;102:1808-25. Epub 2007 Jun 29. Used with permission.*

Antisecretory Treatment

Proton Pump Inhibitors

Proton pump inhibitors are effective for inducing ulcer healing. Once-daily doses of omeprazole, from 20 to 40 mg, result in duodenal ulcer healing in 63% to 93% of patients at 2 weeks and in 80% to 100% at 4 weeks. In most studies, omeprazole has produced more rapid healing than standard doses of H_2-receptor antagonists. Omeprazole at doses of 20 to 40 mg daily also produces greater gastric ulcer healing than H_2 receptor antagonists, but the rate of early healing of gastric ulcers is not accelerated by omeprazole to the same extent as for duodenal ulcers.

Proton pump inhibitors are a group of prodrugs that are acid labile and inactivated when exposed to gastric juice. Most are enteric coated to dissolve at pH >6. After being absorbed, they are concentrated in the secretory canaliculus of parietal cells and irreversibly inactivate the hydrogen-potassium adenosine triphosphatase system, which disrupts the final common pathway for acid secretion. Proton pump inhibitors are the most powerful drugs available to suppress gastric acid secretion. Several important features of clinical relevance need to be stressed:

1. Because there is a significant lag time to peak effectiveness, proton pump inhibitors should not be administered on an "as needed" basis.
2. Because proton pump inhibitors effectively inhibit only stimulated parietal cells, their effectiveness may be diminished by the coadministration of H_2-receptor antagonists.
3. Because proton pump inhibitors inhibit only stimulated parietal cells and parietal cells are stimulated by eating, proton pump inhibitors are most effective when taken shortly before a meal (ie, 30 minutes to 1 hour).

H_2-Receptor Antagonists

In the mid-1970s, H_2-receptor antagonists were shown to heal ulcers in 70% to 85% of patients after 4 to 6 weeks of therapy. Currently, four H_2-receptor antagonists (cimetidine, famotidine, nizatidine, and ranitidine) are available. Although their potency, bioavailability, and side effect profiles differ, they are overall one of the safest classes of drugs available. Single-nocturnal dosing is at least as effective as twice-daily dosing regimens (same total daily dose) in suppressing 24-hour gastric acid secretion and in healing duodenal ulcers. All H_2-receptor antagonists have healing rates for PUD of 90% to 95% at 8 weeks of therapy.

Antacids

Antacids that contain aluminum and magnesium hydroxide effectively heal ulcers by binding bile and inhibiting pepsin. Antacids also promote angiogenesis in injured mucosa. However, at least seven 30-mL doses daily are needed to heal ulcers. This high dose can produce such adverse effects as diarrhea (magnesium-containing agents), constipation (aluminum-containing agents), and sodium overload. Also, calcium-containing antacids can cause acid stimulation and acid rebound.

Sucralfate

Sucralfate is a sulfated polysaccharide that is compounded with aluminum hydroxide. It prevents acute ulceration and heals chronic ulcers without affecting the secretion of gastric acid or pepsin. Like aluminum-containing antacids, sucralfate promotes angiogenesis and the formation of granulation tissue. Because binding of this drug to the ulcer is enhanced at pH <3.5, it should be administered 30 to 60 minutes before meals. From 3% to 5% of this drug is absorbed; thus, there is potential for aluminum toxicity in patients with renal failure. Sucralfate therapy seems to be superior to placebo in healing PUD, but it is not indicated for *H. pylori* infection- or NSAID-induced ulcers, and its effectiveness has not been tested in non-*H. pylori*, non-NSAID ulcers. Therefore, its usefulness in PUD is limited.

Misoprostol

Misoprostol is a prostaglandin E_1 analogue that exerts a mucosal protective effect by stimulating the secretion of mucus and bicarbonate and by enhancing mucosal blood flow. Misoprostol, at doses of 400 to 800 mg daily, enhances duodenal ulcer healing compared with placebo. Misoprostol does not seem to have any advantage over antisecretory agents for ulcer healing. Consequently, it is not indicated for this purpose. The primary role of misoprostol is in the prevention of NSAID-induced gastroduodenal injury. Up to 30% of patients have a dose-dependent diarrhea from stimulation of the

cyclic adenosine monophosphate system. In addition, prostaglandins are uterotropic and may induce bleeding, cramps, and spontaneous abortion in pregnant women. These side effects and limited clinical utility have curtailed the widespread use of misoprostol for both the treatment of PUD and the prevention of NSAID-induced ulceration.

Lifestyle Modifications

Historically, bed rest, milk, and a bland diet were prescribed for PUD. Dietary change is no longer advised. The only general measures recommended are to discontinue cigarette smoking and to avoid NSAIDs. Although certain foods, such as spicy foods and sauces, may increase the dyspeptic complaints of patients, they do not cause ulcer disease or interfere with healing.

FOLLOW-UP AND MAINTENANCE THERAPY

Duodenal Ulcers

Patients with uncomplicated duodenal ulcers without evidence of *H. pylori* infection who have received treatment do not require further endoscopy or radiography to ensure healing unless they have recurrent or persistent symptoms.

Gastric Ulcers

There are no prospective outcome studies to help guide the follow-up of patients who have gastric ulcers. Repeat endoscopy with biopsy has been advocated to confirm gastric ulcer healing to ensure that the ulcer is benign. However, a recent summary of available data showed that more than 98% of gastric cancers associated with ulceration are detected when the initial evaluation includes adequate endoscopic inspection and biopsy. If the initial biopsy findings are negative, the yield of follow-up studies is low. This relies on the adequacy of the initial biopsy specimens. An adequate examination and biopsy require the procurement of at least four biopsy specimens from the ulcer margin and one from the base, if the ulcer is not too deep and it seems safe to do so. The biopsy specimens must contain an adequate amount of tissue.

Because there is no consensus on how to follow-up patients with gastric ulcers, there is a wide range of practice. Generally, patients with ulcers considered at high risk for gastric cancer who require extra vigilance in evaluation and follow-up include those raised in an endemic area with a high prevalence of gastric cancer (eg, East Asia or Central America), those with an ulcer in the absence of NSAID use or *H. pylori* infection, those with a giant ulcer (> 2 cm), and those without a previous ulcer.

Antisecretory Therapy After Eradication of *Helicobacter pylori* Infection

No firm guidelines are available about the continuation of antisecretory medication and management after eradication of *H. pylori* infection in patients with PUD. Some evidence supports the idea that eradication of the infection alone is sufficient to prevent recurrence of PUD. However, two consensus panels have addressed this issue and have recommended maintenance acid-suppression therapy with follow-up after sucessful eradication of *H. pylori* infection in patients with complicated PUD.

Complicated Peptic Ulcer Disease

Patients with complicated PUD at higher risk for nonhealing or recurrent ulcers (eg, ulcers >2 cm, ulcer with fibrotic bed, or significant hemorrhage) also warrant treatment with antisecretory agents, at least until the eradication of *H. pylori* infection has been confirmed and ulcer healing has been established. No studies have had the power to define the best long-term management for these patients. Prolonged antisecretory therapy is likely justified in these patients.

Uncomplicated Peptic Ulcer Disease

For patients with uncomplicated PUD, antisecretory therapy can be discontinued safely after 4 to 6 weeks. Some continued healing may occur with longer treatment periods, but the advantages of prolonged treatment and increased costs for patients who are asymptomatic and uncomplicated are debatable.

PREVENTION OF PEPTIC ULCER DISEASE AND COMPLICATIONS

NSAID-naïve patients who are being considered for long-term NSAID or aspirin therapy should be

evaluated for their risk of PUD. As stated above, there is support for the practice of testing these patients for *H. pylori* infection and, as a preventive measure against PUD, providing eradication therapy if *H. pylori* infection is found. In addition, patients who have risk factors such a previous history of ulcer, advanced age, medications that increase the risk of PUD when taken with NSAIDs (eg, warfarin or glucocorticoids), or other comorbid conditions associated with an increased risk of PUD should be considered for PUD prophylaxis with misoprostol (although the side effects may be limiting) or a proton pump inhibitor.

If possible, NSAIDs should be avoided if patients are taking other drugs that can increase the risk of complicated PUD, for example, platelet aggregation inhibitors, anticoagulants, other NSAIDs such as low-dose aspirin, or corticosteroids.

SUMMARY

PUD is a common disorder worldwide. It usually is caused by *H. pylori* infection or the use of NSAIDs. There are other rare causes of PUD, and most of them are due to hypersecretion of gastric acid.

The cornerstones of treatment for PUD include testing for and, if appropriate, eradicating *H. pylori* infection, discontinuing treatment with NSAIDs if possible, and providing aggressive acid suppression with proton pump inhibitors.

There are some appropriate prevention strategies for PUD. For patients who are at increased risk for the development of PUD because of the requirement of long-term NSAID therapy or who have comorbid conditions or medications that increase the risk of PUD, testing for and eradicating *H. pylori* infection and considering the prophylactic use of proton pump inhibitors are likely useful and cost-effective measures.

RECOMMENDED READING

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CHAPTER 5

Gastritis

Dawn L. Francis, MD, MHS

The term *gastritis* has been used loosely to describe vague endoscopic findings of the gastric mucosa (eg, erythema, nodularity, and erosions) and also to describe gastric inflammation from mucosal injury. This ambiguity has led to confusion about the term "gastritis" in both the clinical setting and the medical literature. Strictly, gastritis refers to the histologic finding of gastric mucosal injury with inflammation. *Gastropathy* is the more appropriate term for epithelial damage without associated inflammation.

Since the discovery of *Helicobacter pylori* and the gastritis associated with it, many attempts have been made to resolve the confusion about the term gastritis, and these attempts have resulted in multiple classification systems. Most classification systems distinguish acute, short-term gastritis from chronic, long-term disease. The terms *acute* and *chronic* are used also to describe the type of inflammatory cell infiltrate. *Acute inflammation* typically is characterized by neutrophilic infiltration, and *chronic inflammation* usually is associated with a preponderance of mononuclear cell infiltration.

In 1994, a group of pathologists met in Houston, Texas, to establish a consistent terminology for *chronic gastritis*. The result is the Sydney System, a classification based on topography, morphology, and etiology (Table 1). Although this is the most referenced system, its complexity has limited its widespread use. Thus, there is no universally adopted classification scheme for gastritis.

Both gastritis and gastropathy are discussed in this chapter. The discussion about gastritis focuses on distinguishing between acute and chronic gastritis and the different causes of gastritis in each of these categories. The discussion about gastropathy focuses on the two most common types: vascular and hypertrophic.

GASTRITIS

Histopathology

The histologic evaluation of gastritis relies on the location, size, and number of biopsy specimens. Because different causes of gastritis can vary topographically in the stomach, it is important to obtain adequate samples of gastric tissue from throughout the stomach. Biopsy specimens should be from both mucosal abnormalities and any surrounding

Abbreviations: CMV, cytomegalovirus; GAVE, gastric antral vascular ectasia; NSAID, nonsteroidal antiinflammatory drug.

Table 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 *H. pylori*	Type A Diffuse corporeal Pernicious anemia
Atrophic-multifocal	*H. pylori*	Type B Environmental Metaplastic Atrophic pangastritis Progressive intestinalizing pangastritis
Chemical/radiation	Bile Nonsteroidal anti-inflammatory drugs Alcohol or other agents? Radiation	Reactive Reflux Radiation
Lymphocytic	Idiopathic Autoimmune Gluten *H. pylori*	Varioliform Celiac-associated
Granulomatous	Crohn's disease Sarcoidosis Wegener's granulomatosis Infectious	Isolated granulomatous
Eosinophilic	Food sensitivities Allergies Idiopathic	Allergic
Infectious gastritides	Bacteria Viruses Fungi Parasites	Phlegmonous Cytomegalovirus Anisakiasis

normal-appearing mucosa. Biopsy specimens from the incisura are often useful because it is the transition zone between the antrum and body and, thus, the location where intestinal metaplasia and atrophy are found most frequently when associated with gastritis. It has been recommended that at least five biopsy specimens be obtained from the stomach: two from the gastric antrum, one from the incisura, and two from the body or fundus (Fig. 1).

In some cases, biopsy specimens from the duodenum may be useful in defining the underlying cause of some types of chronic gastritis. For instance, duodenal biopsy specimens may show celiac disease in patients with lymphocytic gastritis or Crohn's disease in patients with granulomatous gastritis.

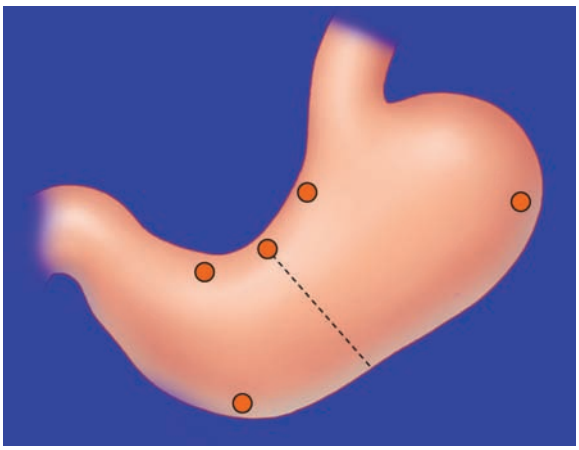

Fig. 1. Gastric biopsy protocol to diagnose gastritis. Biopsy specimens (*red circles*) should be obtained from the greater and lesser curvature of the antrum, incisura (*dotted line*), fundus, and body.

Acute Gastritis

The hallmark of acute gastritis is the development of hemorrhagic or erosive lesions soon after exposure of the gastric mucosa to various toxic substances or immediately following a significant reduction in mucosal blood flow. The most common substances associated with acute gastritis are nonsteroidal antiinflammatory drugs (NSAIDs), alcohol, and bile acids. Various clinical scenarios can result in decreased mucosal blood flow. The most common are trauma, burns, hypothermia, and sepsis. Many cancer therapies, including both radiation and systemic chemotherapy, can injure gastric mucosa directly and cause decreased mucosal blood flow.

Similar to peptic ulcer disease, acute gastritis may be due to an imbalance between injurious and protective factors. The acute mucosal injury that is the hallmark of acute gastritis disrupts the normal protective barrier (mucus, bicarbonate, and the epithelium itself). This permits acid and other damaging luminal substances such as bile acids and proteases to penetrate into the lamina propria, where they cause further damage to the vasculature and incite nerves to release histamines and inflammatory mediators.

NSAIDs produce a topical injury that causes back diffusion of hydrogen ions. Furthermore, NSAIDs have a systemic effect through prostaglandin blockade that decreases bicarbonate release, mucus formation, and mucosal blood flow.

Alcohol causes acute gastritis by disrupting the mucosal microvasculature. Capillary congestion and increased vascular permeability increase the inflammatory cell response and free radical formation, which, in turn, cause mucosal injury.

Acute gastritis due to bile reflux is usually the result of the reflux of bile into the stomach because of a surgical intervention (eg, a Billroth procedure), delayed small-bowel transit, or an incompetent pyloric sphincter. Bile salts and lysolecithin break down the gastric mucosal barrier, which leads to back diffusion of hydrogen ions and mucosal injury.

Hypovolemia or hypotension leads to underperfusion of the gastric mucosa, resulting in the accumulation of vasoactive amines and leukotrienes. This impairs the mucosal barrier and allows the back diffusion of hydrogen ions, leading to further mucosal damage.

Histologically, acute gastritis appears as erosions with features of rapid healing of the mucosal injury. In many cases, a thin regenerative epithelium is the only evidence that erosions had been present.

The most important intervention for acute gastritis is the withdrawal of the offending agent or treatment of the underlying condition (eg, hypotension). The mainstay of treatment is the use of aggressive acid suppression, such as a proton pump inhibitor, to limit injury from gastric acid in the setting of a compromised gastric mucosa.

Chronic Gastritis

Atrophic Gastritis

The term *atrophic gastritis*, or gastric atrophy, has been used for more than a century. It refers to chronic gastritis that is associated with the loss of glands, mucosal thinning, and metaplastic changes of the epithelial cells. Atrophic gastritis has been subcategorized in terms of the role of the immune system (autoimmune, or type A) and functional or endocrine changes in the antrum and body (type B). However, these designations are used inconsistently in the medical literature. Here, atrophic gastritis is subdivided into autoimmune and multifocal types.

Autoimmune Atrophic Gastritis

Autoimmune atrophic gastritis is a form of chronic gastritis associated with severe diffuse atrophy of

the acidophilic glands, chronic inflammation, and epithelial metaplasia. It is the result of an immune response directed against parietal cells and intrinsic factor. The chronic inflammation, gland atrophy, and epithelial metaplasia are paralleled closely by an increase in serum antibodies to parietal cells and intrinsic factor.

The association observed between autoimmune atrophic gastritis and the major histocompatibility haplotypes HLA-B8 and HLA-DR3 has led to the idea that autoimmune atrophic gastritis is a heritable condition. Other conditions in which antibodies to gastric parietal cells have been detected include autoimmune endocrinopathies (eg, Hashimoto's thyroiditis, thyrotoxicosis, myxedema, Addison's disease, and diabetes mellitus) and collagen vascular disease (eg, Sjögren's syndrome).

A causal link has been suggested between *H. pylori* infection and autoimmune gastritis. The evidence supporting this link is the finding that as many as 80% of patients with *H. pylori* infection have autoantibodies directed against the surface membrane of the foveolar epithelium or the canalicular membranes of parietal cells. The development of these autoantibodies is likely due to antigenic mimicry.

Histopathologically, autoimmune atrophic gastritis is characterized by diffuse or focal lymphocytic infiltration, including epithelial lymphocytosis, and associated destruction of oxyntic glands. If metaplasia is present, it is predominantly in the body or fundus. The antrum typically is not affected by metaplasia, but changes consistent with chemical gastropathy are often present.

As a result of the damage to parietal cells, patients with autoimmune atrophic gastritis have various potential clinical manifestations, including achlorhydria, hypergastrinemia, and anemia (which can be due to iron deficiency or malabsorption of vitamin B_{12} or both). In addition to the metaplastic changes associated with autoimmune atrophic gastritis, there is also increased risk of hyperplastic and adenomatous polyps, carcinoid tumors, gastric lymphoma, and gastric adenocarcinoma.

The achlorhydria associated with autoimmune atrophic gastritis can induce hyperplasia of the gastrin-producing G cells, resulting in hypergastrinemia. Gastrin has a trophic effect on endocrine cells in the stomach, which may give rise to hyperplastic nodules. Importantly, carcinoid tumors are thought to arise from the transformation of enterochromaffin-like cells within the oxyntic mucosa as a result of chronic stimulation by gastrin.

Multifocal Atrophic Gastritis

Autoimmune atrophic gastritis is distinct from multifocal atrophic gastritis in that the latter is due directly to the effects of *H. pylori* (ie, not the result of antigenic mimicry). Histologically, multifocal atrophic gastritis is different from autoimmune atrophic gastritis in that there is evidence of bacterial colonization, mature parietal cells, and a monomorphic lymphocytic cell infiltrate. Inflammation is present in both the antrum and body, instead of predominantly in the body and fundus as in autoimmune atrophic gastritis.

When obtaining specimens from a stomach with suspected *H. pylori* infection and associated gastritis, it is important to obtain two specimens from the antrum and two from the body. Specimens from the body are essential because the patient may have received proton pump inhibitor therapy, which causes the organism to relocate from the antrum to the body. A fifth biopsy specimen should be obtained from the incisura because this is the site most likely to show *H. pylori*-associated atrophic gastritis, metaplasia, and dysplasia (Fig. 1).

Chronic Reactive Gastritis

Continuous exposure to substances that injure the gastric mucosa can lead to chronic chemical gastropathy. No endoscopic findings are diagnostic of this condition, and mucosal changes are often confined to the antrum. Histologically, chronic reactive gastritis is typified by variable foveolar hyperplasia, a lack of inflammation (in contrast to *H. pylori*-induced gastritis), edema, an increase in smooth muscle fibers in the lamina propria, and vascular congestion. These changes have been associated with the same substances that induce acute gastritis, namely, bile salts, NSAIDs, and alcohol.

As mentioned above, bile reflux gastritis usually is caused by the reflux of bile into the stomach as a result of a surgical intervention or compromised motility of the upper gastrointestinal tract. The mechanism of injury is the same as for acute gastritis due to bile reflux. Several medical treatments

have been evaluated for bile reflux gastropathy, and none has been particularly successful. Ineffective treatments include cholestyramine in combination with alginates, prostaglandin analogues, and sucralfate. Ursodeoxycholic acid has been helpful in decreasing pain and nausea, but does not produce histologic improvement. The definitive treatment for symptomatic bile acid reflux—when a known predisposing factor exists (eg, previous surgery)—is surgical and usually involves a Roux-en-Y revision. This intervention is associated with symptomatic improvement in 50% to 90% of patients.

As with other toxic substances, NSAIDs can cause both acute gastritis and chronic gastritis. It is known that a portion of patients will have a reduction in the acute changes (erosions or hemorrhagic gastritis) associated with NSAIDs because of mucosal adaptation to the injury. However, many patients who take NSAIDs will continue to have ulcerative or inflammatory lesions, including gastric or duodenal ulceration in 15% of them.

It is clear that ingested alcohol (ethanol) can be toxic to the gastric mucosa. Alcohol has been associated with acute gastric hemorrhage and erosive gastropathy in animal models and humans. However, it is not entirely clear that alcohol causes chronic gastritis. The effects of alcohol on the stomach over the long term are difficult to study because many patients who use alcohol may have other risk factors for the development of chronic gastritis, including *H. pylori* infection, NSAID use, and smoking. Most of the studies that evaluated the association between alcohol ingestion and chronic gastritis were performed before the discovery of *H. pylori* and, thus, have limited applicability.

Infectious Gastritis

Bacterial Infections

H. pylori infection is the major cause of chronic gastritis worldwide. Rarely is acute gastritis associated with *H. pylori* encountered clinically because the acute illness is mild, transient, and usually asymptomatic. *H. pylori* infection can cause both atrophic and nonatrophic gastritis.

H. pylori is a gram-negative helical-shaped bacterium that has four to six flagella. These bacteria colonize only the gastric epithelium. When they are found elsewhere in the gastrointestinal tract (eg, the gastroesophageal junction or the duodenum), they are associated with metaplastic gastric epithelium.

H. pylori can be detected in both the antrum and the body of the stomach in the majority of patients (80%). In 10% of patients, the organism is found only in the gastric body. The reason for this is not entirely clear, but one theory is that *H. pylori* migrate to the body of the stomach in patients who are taking proton pump inhibitors because of the suppression of *H. pylori* growth in the antrum.

The histologic characteristics of chronic *H. pylori* gastritis are well defined. Typically, there is a concentration of inflammatory cells (lymphocytes, plasma cells, scattered macrophages, and often an increased number of eosinophils) in the upper part of the mucosa just below the surface epithelium. This creates the appearance of a superficial gastritis, especially in the oxyntic mucosa. Frequently, lymphoid follicles are present and are considered pathognomonic for *H. pylori* infection. The lymphoid follicles that result from *H. pylori* gastritis are the precursors to primary gastric lymphoma.

Several other species of bacteria can cause chronic gastritis. These usually reside in the stomach after antrectomy or in association with achlorhydria. *Streptococcus*, *Staphylococcus*, *Lactobacillus*, *Bacteroides*, *Klebsiella*, and *Escherichia coli* have all been cultured from gastric fluid, but they rarely have clinical significance. In certain circumstances, such as with severe immunosuppression or ischemia, these bacteria may produce marked morbidity. For example, phlegmonous gastritis is a life-threatening condition associated with full-thickness purulent necrosis that invades the gastric wall.

Viral Infections

Cytomegalovirus (CMV) is the most common virus associated with gastritis. CMV can infect any cell within the gastrointestinal tract, including the stomach. In the stomach, CMV infection usually causes ulceration, but the endoscopic findings can be vague. Biopsy specimens show mucosal inflammation, vascular endothelial involvement, and even tissue necrosis. The characteristic cytomegalic cells (large cells with eosinophilic intranuclear inclusions) are present.

CMV infection is considered an opportunistic infection and is usually, but not always, diagnosed in the presence of immunodeficiency. Patients with

acquired immunodeficiency syndrome are prone to this infection when the CD4 count is less than 100. Patients receiving immunosuppressive therapy for a solid-organ or bone marrow transplant are also at risk.

The three antiviral agents that can be considered for the treatment of CMV gastritis are foscarnet, ganciclovir, and valganciclovir. Valganciclovir is used most commonly because of its high oral bioavailability, as opposed to foscarnet and ganciclovir that are administered intravenously. Valganciclovir is a valine ester of ganciclovir and is absorbed rapidly and hydrolyzed to ganciclovir. A daily dose of 900 mg of valganciclovir is equivalent to 5 mg/kg of ganciclovir administered intravenously.

Patients with CMV infection of the gastrointestinal tract should receive 6 weeks of induction antiviral therapy. It is unclear whether they then should receive maintenance antiviral therapy, as for other CMV infections such as CMV retinitis.

Mycobacterium

Mycobacteria may involve the stomach and cause gastritis in patients with disseminated tuberculosis or systemic *Mycobacterium avium-intracellulare* infection. Patients with tuberculosis have the pathognomonic necrotizing granulomas seen on histology. Gastric infection with *M. avium-intracellulare* is characterized by an accumulation of foamy histiocytes that stain positive for acid-fast bacilli. Treatment is targeted at treating the systemic infection.

Syphilitic Gastritis

Treponema pallidum can cause chronic gastritis in the second and third stages of the infection. Endoscopically, this infection may look like erosive antral gastritis. In some cases, thick gastric folds may form from infiltration by mononuclear plasma cells and may have an appearance that suggests linitis plastica or lymphoma. Syphilitic gastritis also may cause a granulomatous gastritis. Because spirochetes generally are difficult to identify, testing for evidence of systemic infection is often required to make the diagnosis.

Fungal Infection

Although *Candida* species are known to colonize gastric ulcers, *Candida* has not been shown to cause primary gastritis. Rarely, opportunistic fungi have caused severe necrotizing gastritis, including mucormycosis in patients with diabetes mellitus. *Torulopsis glabrata* and *Cryptococcus neoformans* have been reported to cause gastritis in patients with immunosuppression.

Special Forms of Gastritis

Lymphocytic Gastritis

Lymphocytic gastritis is often asymptomatic and is diagnosed when biopsy specimens are taken from normal, or only slightly abnormal, appearing gastric mucosa (Fig. 2). The essential diagnostic feature is infiltration of the surface epithelium with lymphocytes. The lymphocytes are usually T lymphocytes, mostly CD8 cells, with cleaved nuclei and a small amount of cytoplasm. The lymphocytic infiltration is present in both the body and antrum.

Lymphocytic gastritis is frequently encountered in patients with *H. pylori* infection and in adult and pediatric patients with celiac disease. In a large series of patients with biopsy-confirmed lymphocytic gastritis, 38% had celiac disease, 29% had *H. pylori* infection, and the rest had various other intestinal conditions. The rate of celiac disease among patients with lymphocytic gastritis is so high that finding lymphocytic gastritis in a patient who is not known to have celiac disease should prompt clinical consideration of occult celiac disease.

Granulomatous Gastritis

Various infectious and noninfectious diseases can cause granulomatous gastritis. Endoscopically, granulomatous gastritis may appear as mucosal nodularity, thickened folds, or even ulcers. When granulomatous gastritis has an infectious cause (eg, tuberculosis, histoplasmosis, or syphilis), the underlying infection usually has been identified already in other tissues. Granulomatous gastritis also may result from noninfectious conditions such as Crohn's disease, sarcoidosis, Wegener's granulomatosis or, rarely, gastric neoplasm. Treatment is aimed at the underlying systemic infection or illness.

Eosinophilic Gastritis

Eosinophilic gastritis is due to eosinophilic infiltration that may involve the full thickness of the stomach. In this disorder, the gastric antrum is

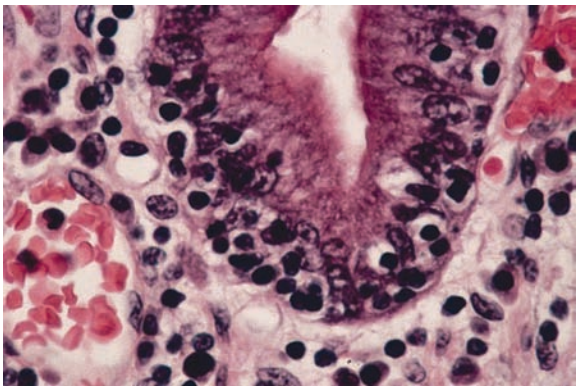

Fig. 2. Lymphocytic gastritis. Intraepithelial lymphocytes can be seen without any destruction of surrounding epithelial cells. (From Owen DA. Gastritis and carditis. Mod Pathol. 2003;16:325-41. Used with permission.)

involved more often than the body or fundus. As with granulomatous gastritis, the gastric mucosa can show nodularity or thickened mucosal folds.

Several diseases can be associated with a small number of eosinophils in the stomach. However, eosinophilic gastritis should be diagnosed only when a large number of eosinophils form a sheetlike monomorphic distribution.

Eosinophilic gastritis has been associated with connective tissue disorders such as scleroderma. It has been seen also with infiltration of the wall of the stomach by parasitic larvae, as in anisakiasis. However, most cases of eosinophilic gastritis are idiopathic. Peripheral blood eosinophilia is found in up to 75% of patients. The disease typically responds to systemic corticosteroid therapy.

GASTROPATHY

Vascular Gastropathies

Vascular gastropathies are abnormalities in the gastric tissue that involve the mucosal vessels, with little or no inflammation. The two most important vascular gastropathies are *gastric antral vascular ectasia* (GAVE), or watermelon stomach, and *portal hypertensive gastropathy*.

Gastric Antral Vascular Ectasia

GAVE is characterized by longitudinal columns of vascular ectasias that cross the antrum and converge on the pylorus. The columns have the appearance of the outside of a watermelon, which has led to this disorder commonly being referred to as *watermelon stomach* (Fig. 3). Histopathologic examination of GAVE shows minimal inflammation in the lamina propria, but there is prominent fibromuscular hyperplasia and dilated mucosal capillaries.

GAVE is more common in females, and is associated with collagen vascular diseases and liver disease. Patients with GAVE can develop iron deficiency anemia and may become transfusion dependent. For these patients, GAVE can be treated endoscopically with argon plasma coagulation, with treatment repeated until the abnormality is obliterated (Fig. 3). Patients with underlying liver disease usually benefit from liver transplantion, but a transjugular intrahepatic portosystemic shunt does not seem to be helpful. Patients without liver disease who have refractory bleeding from GAVE despite endoscopic therapy may require antrectomy.

Portal Hypertensive Gastropathy

Portal hypertensive gastropathy appears as a mosaic pattern of the mucosa that usually is more pronounced in the fundus and body of the stomach (Fig. 4). As the name suggests, this gastropathy is associated exclusively with portal hypertension. Compared with GAVE, the vascular abnormalities involve deeper submucosal vessels that are dilated, irregular, and tortuous.

Portal hypertensive gastropathy is graded endoscopically as mild or severe. Severe portal hypertensive gastropathy has active oozing or hemorrhage. Patients with severe portal hypertensive gastropathy may develop iron deficiency anemia and require blood transfusion. Because deep submucosal vessels are involved in this disorder, there is no effective endoscopic treatment. Treatment is aimed at decreasing portal hypertension and, thus, may involve the administration of nonselective β-blockers, portal decompression (such as transjugular intrahepatic portosystemic shunt), or liver transplantation.

Hypertrophic Gastropathy

When large gastric folds are observed on endoscopy, the general term *hypertrophic gastropathy* has been applied. Several infiltrative, proliferative, and inflammatory conditions are associated with large

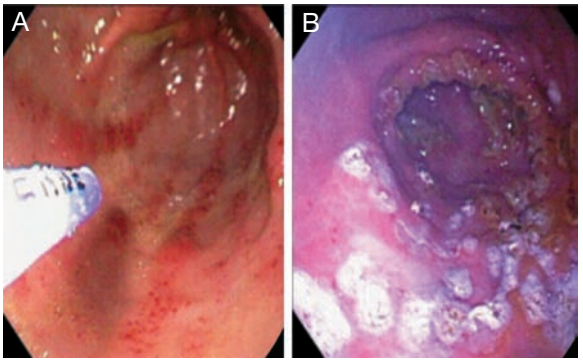

Fig. 3. Gastric antral vascular ectasia (GAVE) with argon plasma coagulator. *A*, Before treatment. *B*, After treatment. (Courtesy of Dr. Louis M. Wong Kee Song, Gastroenterology and Hepatology, Mayo Clinic. Used with permission.)

mucosal folds in the stomach. The most common is chronic gastritis, which is the cause of 40% of cases of hypertrophic gastropathy. Other causes include benign and malignant tumors (approximately 30% of cases), hypertrophy associated with Zollinger-Ellison syndrome, and Ménétrier's disease, which accounts for fewer than 10% of cases in which large gastric folds are observed.

Ménétrier's Disease

Patients with Ménétrier's disease may have various nonspecific clinical features such as abdominal pain, weight loss, nausea, diarrhea, or protein-losing enteropathy. The diagnosis requires a full-thickness gastric biopsy specimen or biopsy via endoscopic snare of an enlarged fold. Histologic examination shows extreme foveolar hyperplasia with glandular atrophy.

There is no proven treatment for Ménétrier's disease. According to one case report, the administration of subcutaneous octreotide showed improvement in enteral protein loss. Patients who have severe hypoalbuminemia, pyloric obstruction, intractable pain, or in whom malignancy is a concern and cannot be excluded may warrant gastric resection.

SUMMARY

When applied precisely, the term *gastritis* describes inflammation in the gastric mucosa due to mucosal injury. Broadly, gastritis can be divided into acute and chronic gastritis and then subdivided on the basis of the cause of the mucosal injury. Gastritis may have various appearances on endoscopy, including erosions, erythema, nodularity, or thickened gastric folds. Diagnosis is based on histologic findings and the clinical history. Treatment usually is targeted at withdrawing the offending agent or treating an underlying infection or systemic disease.

The term *gastropathy* denotes epithelial damage without associated inflammation. The two most common types of gastropathy are vascular and hypertrophic. Like gastritis, the diagnosis is made on the basis of histopathologic findings. For vascular gastropathies, treatments include endoscopic therapy for GAVE complicated by anemia and treatment of the underlying portal hypertension in patients with portal hypertension gastropathy. Oftentimes, hypertrophic gastropathy can be treated by addressing the underlying disease. However, Ménétrier's disease has no known treatment and, when severe, may require surgical intervention.

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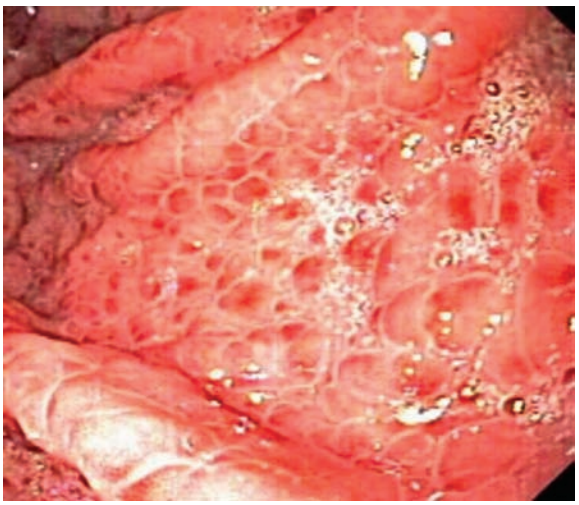

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CHAPTER 6

Gastric Neoplasms and Gastroenteropancreatic Neuroendocrine Tumors

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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, neuroendocrine tumors, and metastatic disease involving the stomach (Table 1). This chapter considers the epidemiology, pathogenesis, clinical presentation, diagnostic evaluation, treatment, and prognosis of these neoplastic diseases.

Table 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
Gastroenteropancreatic neuroendocrine tumors (including carcinoids), gastrointestinal stromal tumors, and metastatic disease to the stomach	<5

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 deadly of malignancies. Currently, gastric adenocarcinoma is the second most common cancer worldwide, with approximately 870,000 new cases and 650,000 deaths per year. Gastric cancer mortality rates have remained relatively unchanged over the past 30 years, and gastric cancer continues to be one of the leading causes of cancer-related

Abbreviations: BAO, basal acid output; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; ENMZL, extranodal marginal zone B-cell lymphoma; EUS, endoscopic ultrasonography; GIST, gastrointestinal stromal tumor; GNET, gastroenteropancreatic neuroendocrine tumor; MALT, mucosa-associated lymphoid tissue; MEN, multiple endocrine neoplasia; VIP, vasoactive intestinal polypeptide.

death. Gastric cancer is rare before the age of 40 years, but its incidence climbs steadily thereafter and peaks in the seventh decade of life.

The incidence of gastric cancer varies by geographic location. Sixty percent of gastric cancers occur 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: North America, Northern Europe, and Southeastern Asia. Regardless of region, gastric cancer is more common in men than in women.

Although gastric cancer is relatively infrequent in North America, it contributes substantially to the burden of cancer deaths, being the third most common gastrointestinal malignancy after colorectal and pancreatic cancer and the third most lethal neoplasm overall.

The worldwide incidence of gastric cancer has decreased over the past few decades. Gastric cancer used to be the leading cause of cancer mortality 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 *H. pylori* infection and changes in diet 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 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 mortality 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. The most widely accepted model for the development of gastric cancer is the progression from chronic gastritis to the development of intestinal metaplasia, dysplasia, and, ultimately, adenocarcinoma.

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 used commonly before the era of refrigerators. Regions that use nitrate-based fertilizers also have a higher incidence of gastric cancer.

Diets high in salt have also 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 provided by fruits and vegetables is thought to be due to their vitamin C content, which may decrease the formation of nitroso compounds inside the stomach.

Tobacco Use

Smoking increases the risk of gastric cancer. This risk decreases after 10 years of smoking cessation. Socioeconomic status also affects the risk of gastric cancer. Distal cancer is twofold 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 are at higher risk for the development of gastric cancer. This risk is greatest 15 to 20 years after the operation. Billroth II surgery carries a higher risk than the Billroth I surgery, 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 two infections that have been associated with an increased risk of the development of gastric cancer are Epstein-Barr virus infection and *Helicobacter pylori* infection. Epstein-Barr virus infection has been associated with various malignancies, the most common being nasopharyngeal carcinoma. It has been estimated that 5% to 10% of gastric cancers are associated with Epstein-Barr virus infection.

H. pylori infection of the human stomach is the most important risk factor for the development of gastric cancer. Whereas persistent viral infection leads to several cancers, *H. pylori* was the first bacteria linked to a human cancer. *H. pylori* has been classified as a definite carcinogen by the World Health Organization. The infection likely triggers inflammation that results in atrophy and may progress to intestinal metaplasia, dysplasia, and cancer. Although few patients with *H. pylori* infection develop gastric cancer, 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 mucus 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, which leads to atrophic gastritis. *H. 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 twofold 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 the gene encoding the cell adhesion protein E-cadherin leads to an autosomal dominant predisposition to gastric carcinoma, referred to as *hereditary diffuse gastric cancer*, that has a penetrance of approximately 70%. It has been suggested that identification of the E-cadherin mutation should prompt prophylactic gastrectomy in affected kindreds.

Also, certain cancer syndromes have been associated with gastric cancer, including 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 are at an increased risk for the development 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

The clinical features of gastric cancer are vague. Patients often complain of epigastric pain, early satiety, abdominal bloating, or meal-induced dyspepsia. Weight loss, nausea, and anorexia are common with advanced lesions. Patients with cancer involving the distal antrum or pylorus may

have 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.

Gastric cancer spreads by direct extension through the stomach wall to perigastric tissue, and it invades adjacent structures, including the pancreas, colon, spleen, kidney, or 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's node), periumbilical area (Sister Mary Joseph's 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 Lesar-Trelat (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 have a worse prognosis, stage for stage, than distal cancers—a finding that suggests 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 of gastric cancer may be the change during the past 20 years in the distribution of cancers from the body and antrum to the proximal stomach. Cancers involving the proximal stomach and gastroesophageal junction have 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 areas with a high incidence of gastric cancer, whereas cardia cancers are more prevalent in populations with a low incidence of gastric cancer.

Infiltration

The linitis plastica lesion occurs in up to 10% of gastric adenocarcinomas. 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 two types: intestinal and diffuse. The intestinal type of 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 countries with a high incidence of gastric adenocarcinoma. It often arises within an area of intestinal metaplasia. This pathologic variant generally has a better prognosis than the diffuse type.

The diffuse type of 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 (Fig. 1). The diffuse type occurs more commonly in younger persons, is less likely to be associated with intestinal metaplasia, and tends to be infiltrating, poorly differentiated, and generally has a poor prognosis.

Staging

At presentation, 65% of gastric cancers in the United States are at an advanced stage. The most important aspect of staging is determining whether the cancer is resectable. Staging is both clinical and pathologic. 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 is used most frequently (Table 2). Preoperative staging of patients with gastric cancer includes physical examination; computed

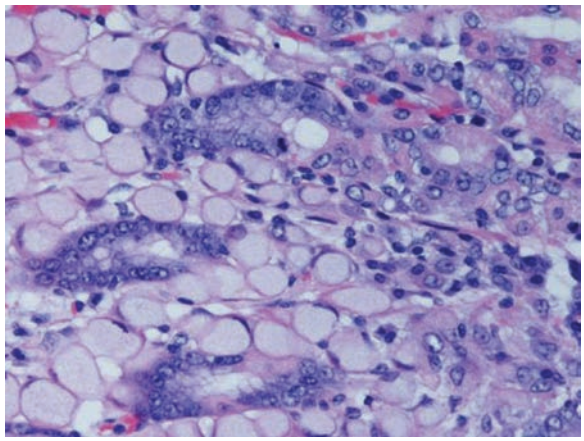

Fig. 1. Diffuse type of gastric adenocarcinoma with mucus-producing signet ring cells. (Courtesy of Dr. Thomas C. Smyrk, Anatomic Pathology, Mayo Clinic.)

tomography (CT) of the chest (for proximal lesions), abdomen, and pelvis; and endoscopic ultrasonography (EUS).

Treatment

Surgery is the mainstay of treatment for gastric cancer. Complete surgical removal of a gastric tumor, with resection of the adjacent lymph nodes, is 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% in 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 a more extensive resection than those in the distal stomach. Palliative rather than curative surgery may still be considered in certain circumstances, for example, for tumor obstruction, perforation, and bleeding.

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

Table 2. The TNM Staging System for Gastric Adenocarcinoma

Tumor (T) stage	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1s	Carcinoma in situ
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria or subserosa
T3	Tumor penetrates serosa without invading adjacent structures
T4	Tumor invades adjacent structures
Nodal (N) stage	
NX	Regional nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in 1-6 regional lymph nodes
N2	Metastasis in 7-15 regional lymph nodes
N3	Metastasis in more than 15 regional lymph nodes
Metastasis (M) stage	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Prognosis

Even with more advanced surgical techniques and chemotherapeutic agents, the prognosis for gastric adenocarcinoma remains grim for all but those who are candidates for surgical resection. Prognosis after resection varies according to the pathologic extent of disease and the population studied. In general, 5-year survival rates can be

approximated as follows: stage IA, 80%-95%; IB, 60%-85%; II, 30%-50%; IIIA, 20%-40%; IIIB, 10%; and IV, 7%.

GASTRIC LYMPHOMA

Epidemiology

Primary gastric lymphoma accounts for up to 10% of lymphomas and up to 5% of gastric neoplasms. 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 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.

In the stomach, the most frequent lymphomas are low-grade extranodal marginal zone B-cell lymphomas (ENMZLs) (formerly known as mucosa-associated lymphoid tissue [MALT] lymphomas) and diffuse large B-cell lymphomas (DLBCLs).

Risk Factors

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

Clinical Features

The clinical features of gastric lymphoma are nonspecific and may include abdominal discomfort, dyspepsia, gastric outlet complaints due to obstruction or impairment of gastric motility, anorexia, weight loss, and anemia due to blood loss from ulceration.

Diagnostic Evaluation

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

When the disease is suspected, standard endoscopic biopsy specimens may be inadequate or the histologic findings equivocal, especially when the involvement is primarily submucosal. 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 one small series, superficial spreading or diffuse infiltrating type lesions on EUS were due to ENMZLs and mass-forming lesions were associated with DLBCLs.

Tumor Features

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 in recent years, it has been classified as a specific subtype of non-Hodgkin's 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. *H. 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 for *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's lymphoma. DLBCL may occur de novo, but it may also 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 [Fig. 2]). Generally, stage I disease is limited to the stomach and stage II disease implies localized involvement of the lymph nodes on the same side of the diaphragm. In stage III disease, both sides of the diaphragm are involved. 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.

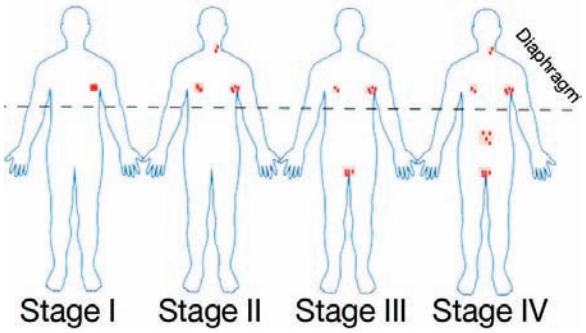

Fig. 2. Staging diagram for lymphoma. *Orange boxes*, lymph nodes involved. (From http://www.lymphomation.org/stage.htm. c2004 [cited 2007]. Used with permission.)

Once treatment for *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, radiation, or surgery, should be administered. Patients who do not initially have a response to or who have disease relapse after anti-*H. pylori* 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 radiation. Generally, the standard of care for localized gastric ENMZL that does not respond to antibiotic therapy or is *H. pylori*-negative is radiotherapy, which has more than a 90% survival rate at 5 years. 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 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 sytemic 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 with nodal DLBCL. This study demonstrated improved response rates and survival for the patients randomly assigned to the R-CHOP regimen.

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 tumors affecting the gastrointestinal tract are divided into two groups: tumors identical to those that arise in soft tissues throughout the rest of the body (lipomas, hemangiomas, schwannomas, leiomyomas, and leiomyosarcomas) and tumors referred to as *gastrointestinal stromal tumors* (GISTs). GISTs can occur anywhere in the gastrointestinal tract but usually affect the stomach and proximal small intestine.

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 6,000 cases annually (10-20 cases per million population). 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 into a clinically relevant size.

Pathogenesis

Originally, it was thought that GISTs arose solely 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. Of importance, 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 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 potential for malignant behavior.

Clinical Features

GISTs are often asymptomatic and 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 II 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, it 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 primarily involves 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 (Fig. 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 intravenous contrast.

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. However, if metastatic disease is present, surgical biopsy may be necessary to confirm the diagnosis if chemotherapy is a consideration.

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, 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 will remain free of disease over 5 years. For patients with recurrent disease, locally advanced disease, or metastatic disease, the response rate with imatinib is approximately 80%. Imatinib is not a cytotoxic agent, 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 worse than stomach), tumor size (the larger, the worse the prognosis), 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 over the past decade, 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.

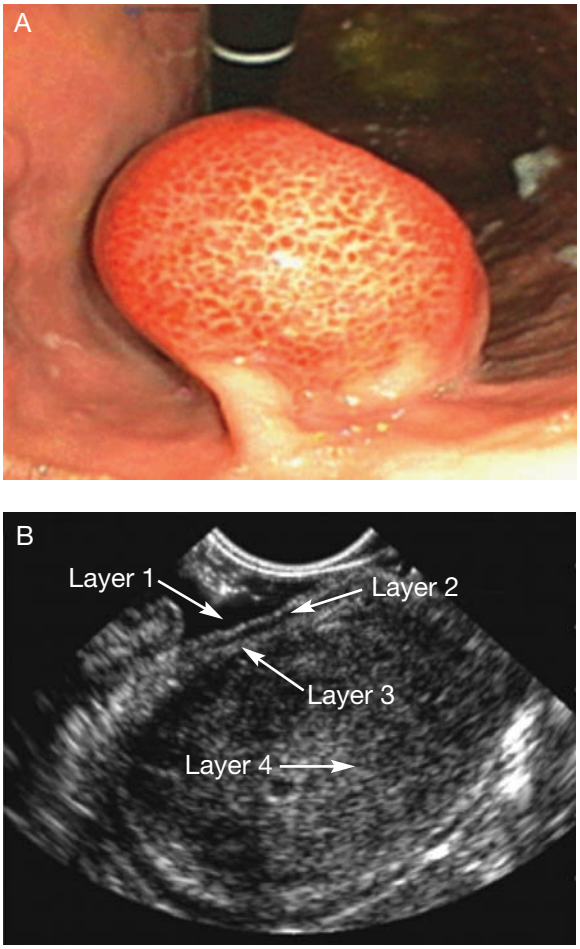

Fig. 3. *A*, Endoscopic and, *B*, endoscopic ultrasonographic images of a pedunculated gastric gastrointestinal stromal tumor. Endoscopic ultrasonography can demonstrate five wall layers, but only four layers are seen in *B*. Layer 1 is hyperechoic (white) and is the superficial mucosa interface. Layer 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 Dr. Michael J. Levy, Gastroenterology and Hepatology, Mayo Clinic.)

GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS

Gastroenteropancreatic neuroendocrine tumors (GNETs) arise from neuroendocrine cells. Neuroendocrine cells occur throughout the body, and neoplasms arise from these cells in many locations. GNETs have variable biologic behavior and are categorized as poorly differentiated neuroendocrine tumors (such as small cell carcinoma of the lung) and well-differentiated neuroendocrine tumors. The poorly differentiated tumors are high-grade malignancies that usually do not occur in the gastrointestinal tract. The well-differentiated tumors typically are indolent, and most occur in the gastrointestinal tract. In the gastrointestinal tract, GNETs include carcinoid tumors and pancreatic islet cell tumors (gastrinoma, insulinoma, glucagonoma, VIPoma, and somatostatinoma).

Epidemiology

GNETs are uncommon. Of these tumors, carcinoid tumors are the most common, with an annual incidence of 15 per 1,000,000 population. In the United States, all other GNETs combined have a prevalence of 10 per 1,000,000 population.

Pathogenesis

GNETs may occur sporadically or as part of an autosomal dominant inherited multiple endocrine neoplasia (MEN) syndrome. All gastrointestinal endocrine tumors can be associated with MEN type 1 (MEN 1). MEN 1 is characterized by pituitary, parathyroid, and pancreatic hyperplasia or tumors.

Clinical Features

Because GNETs are of neuroendocrine origin, they may secrete various peptides and hormones. Most of these tumors produce several hormones, but very few are associated with a clinical syndrome. They also produce substances other than peptides, for example, chromogranins, which can be localized with immunochemical studies.

CARCINOID TUMORS AND CARCINOID SYNDROME

Carcinoid tumors, the most common GNETs, are slow growing and can occur anywhere in the alimentary tract. The clinical presentation 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.

Carcinoid tumors are rare, and those that cause carcinoid syndrome are even rarer. Only 5% of patients with carcinoid tumors have carcinoid syndrome. When the syndrome is present, it is associated most commonly with tumors in the small bowel that have metastasized to the liver.

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 often inactivates 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. The most common physical finding is hepatomegaly. Intermittent facial flushing occurs in up to 85% of the patients. The flush usually starts acutely 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. Below, each of these characteristics is discussed according to the organ from which the tumor arises (Table 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 and 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 long period should alert clinicians that gastric carcinoid tumors may be present.

Gastric carcinoids have been divided into three separate 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 fewer 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

Table 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, descending, and sigmoid colon and rectum	None	Rare	Indolent except in colon

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 the 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 at the time the tumor is discovered. Type 3 is the only type of gastric carcinoid that is associated with carcinoid syndrome, because these tumors often produce 5-hydroxytryptophan. Because sporadic gastric carcinoids (type 3) are more aggressive, they usually are treated by 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

Small intestinal carcinoid tumors are the carcinoid tumors most important clinically 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 2 ft 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 small intestinal carcinoids, regardless of size, have the potential to metastasize, they should be removed surgically, with local lymph node resection. These are the patients most at risk for synchronous lesions (present in 30% of cases), so at the time of 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 half of intestinal carcinoids are appendiceal tumors, and carcinoid tumors are the most common neoplasms of the appendix. They are almost always asymptomatic and typically 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 of 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 is almost always in the setting of liver metastases.

The prognosis of 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. Larger tumors usually can be treated with right hemicolectomy.

The overall 5-year survival rate of 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, patients 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

Rectal carcinoids nearly always are asymptomatic and 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 Syndrome

Most carcinoid tumors are found incidentally on endoscopy or imaging studies performed for other indications. If symptoms are present and are due to local effects of the tumor, they usually are found on CT. If symptoms of carcinoid syndrome are strongly suspected, the best initial evaluation is with urinary 5-hydroxyindoleacetic acid. Carcinoid tumors lack aromatic L-amino acid decarboxylase; thus, urinary levels of 5-hydroxyindoleacetic acid are increased. Octreotide scintigraphy (Octreascan) identifies the site of primary tumors and metastatic disease in more than 80% of patients with carcinoid syndrome. Magnetic resonance imaging and selective angiography are sensitive for detecting metastases to the liver.

GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS OF PANCREATIC ORIGIN

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 fewer than 1% of patients who have peptic ulcer disease. Gastrinomas are frequently associated 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, we now know that extrapancreatic gastrinomas are common. One-half of gastrinomas occur in the duodenal wall; the pancreas is the second most common site. However, more than 90% of gastrinomas occur in an anatomical area called the *gastrinoma triangle* (Fig. 4).

Gastrinomas are slow growing, and it can be difficult to differentiate 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 (Fig. 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

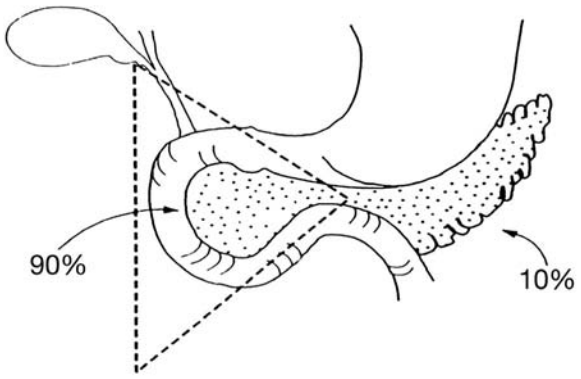

Fig. 4. The gastrinoma triangle. Note that 90% of gastrinomas occur inside the gastrinoma triangle.

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.

Diagnostic Tests

For patients with the clinical manifestations of gastrinoma, the first screening test is determining 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 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, or 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, or a rare hereditary condition called *antral G-cell hyperplasia*.

If the gastrin level is increased, then it must be determined whether there is concomitant gastric acid hypersecretion. This is done by measuring basal acid output (BAO). Before BAO is measured, acid-suppressing medications must be discontinued: 24 hours for H_2-receptor antagonists and 7 days for proton pump inhibitors. In the 24 hours before the test, the patient receives antacids. A nasogastric tube is placed into the antrum, and the stomach is emptied. Four samples of gastric fluid are collected; a quadruplicate of each sample is

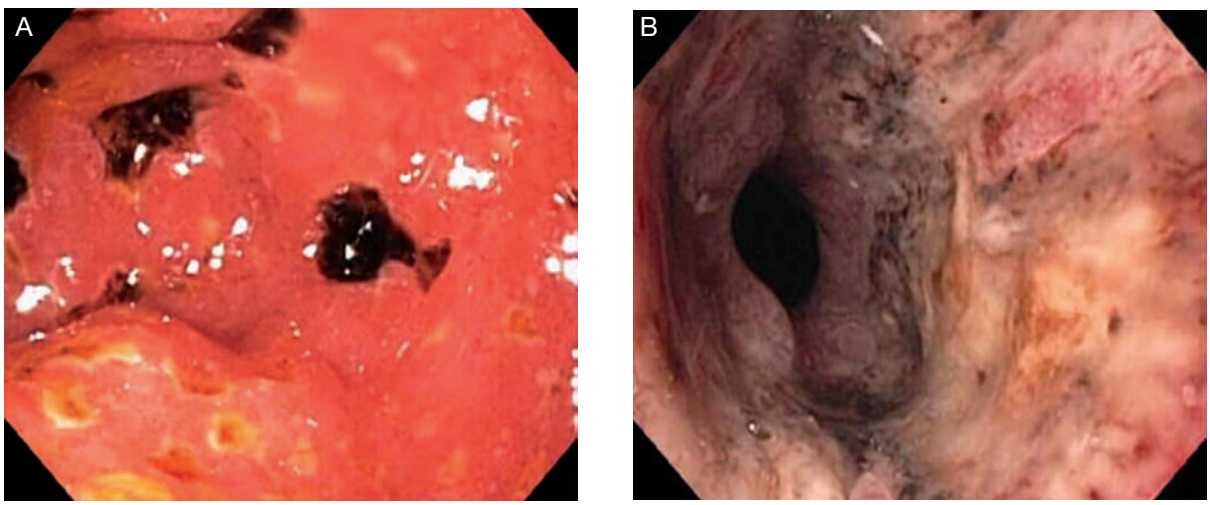

Fig. 5. Endoscopic images of, *A*, multiple duodenal ulcers and, *B*, severe esophagitis in a patient with metastatic gastrinoma who receives proton pump inhibitor therapy.

titrated to pH 7 with 0.2 N sodium hydroxide, while the BAO is determined with a radiometer titrator. In a stomach that has not been operated upon, a BAO greater than 15 mEq/hour is diagnostic of Zollinger-Ellison syndrome. If the patient underwent gastric resection for acid reduction, a BAO greater than 10 mEq/hour is diagnostic of Zollinger-Ellison syndrome.

A secretin stimulation test is warranted for only a few clinical situations (Fig. 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.

Once there is biochemical evidence of gastrinoma, the tumor should be localized. Most gastrinomas have somatostatin receptors. Thus, the radiolabeled somatostatin analogue octreotide used with scintigraphy 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 proton pump inhibitors and octreotide.

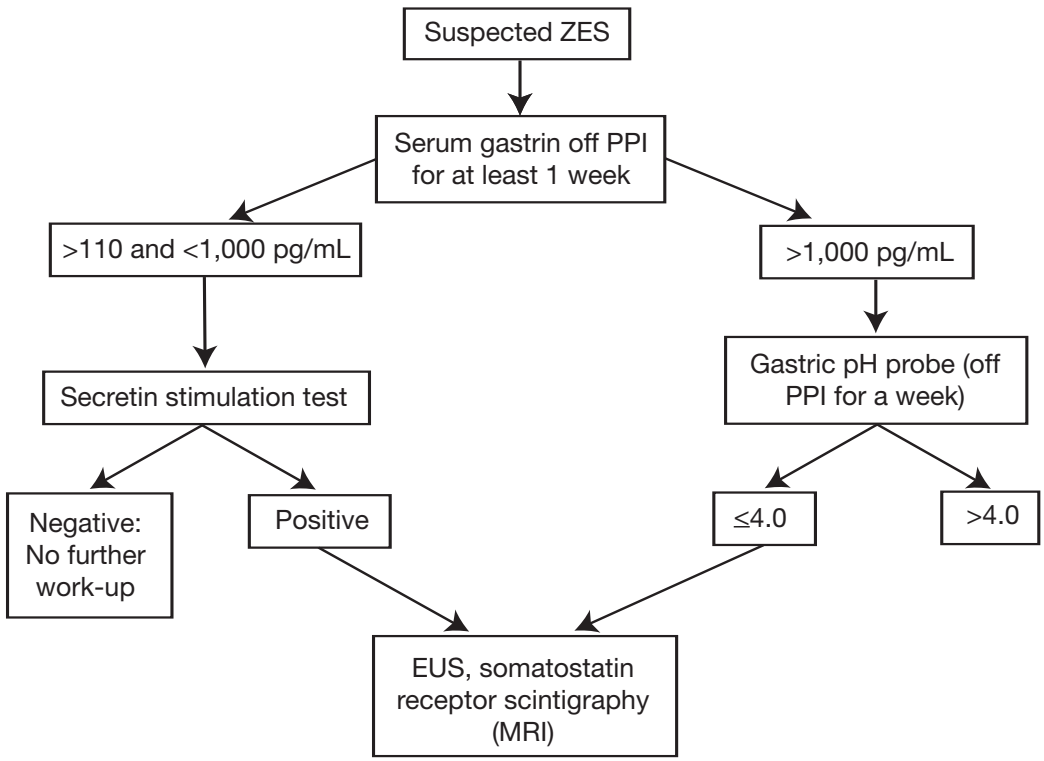

Fig. 6. Diagnostic evaluation of gastrinoma and Zollinger-Ellison syndrome (ZES). EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; PPI, proton pump inhibitor.

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.

Clinical Features

Most patients present with clinical manifestations of hypoglycemia: altered or loss of consciousness, confusion, dizziness, and visual disturbances. Symptoms may also result 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 insulin level. This combination is identified in 65% of patients with insulinoma. For a definitive diagnosis, a 72-hour fast is required, with serum glucose and insulin levels 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, radiolabeled octreotide with scintigraphy 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, so EUS can detect nearly 90% of them. EUS is the imaging modality of choice. Metastatic insulinoma is evaluated best with magnetic resonance imaging.

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 a neuroendocrine tumor that is usually in the pancreas and produces vasoactive intestinal polypeptide (VIP). This syndrome is characterized by severe watery diarrhea, hypokalemia, and achlorhydria and is known as the *WDHA syndrome* (watery diarrhea, hypokalemia, and achlorhydria), 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. A VIPoma usually is a solitary non-beta pancreatic islet cell tumor, 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. Seventy-five percent of VIPomas are malignant, and 50% have metastasized at the time of diagnosis. VIPomas cannot be differentiated 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. VIP induces intestinal water and chloride secretion and inhibits gastric acid secretion.

Clinical Features

As stated above, VIPomas cause secretory diarrhea, which results in hypokalemia and dehydration. Stool volume may exceed 3 L/day. The watery diarrhea resembles that of cholera, hence the term *pancreatic cholera*. Erythematous flushing of the head and trunk may occur in some patients. Also,

some patients develop hyperglycemia 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 somatostatin receptor scanning 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 5 L or more of fluid per day, with aggressive potassium replacement. Long-acting octreotide controls the 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 without 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. Streptozocin plus doxorubicin or fluorouracil are the most effective chemotherapy regimens and achieve 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. Sixty-five percent of the tumors 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. The characteristic presentation is that of 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 some 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 objective of treatment is to control the symptoms and hyperglycemia and to restore nutritional status. The surgical risk of 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.

In 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 and 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 neuroendocrine tumors 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 the 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 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. 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 OF GNETS

In general, the treatment of GNETs 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 the symptoms of carcinoid syndrome (Fig. 7).

The liver is the predominant site of metastatic disease. Hepatic 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. Patients with flushing

should avoid ingesting substances that can induce flushing, such as alcohol. 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 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 monthly, rather than thrice daily, administration. 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 and doxorubicin or fluorouracil) have been tried in various combinations and generally have had minimal effect on these tumors. The lack of effectiveness of any one agent or combination of agents has led to debate about whether chemotherapy is appropriate for these patients.

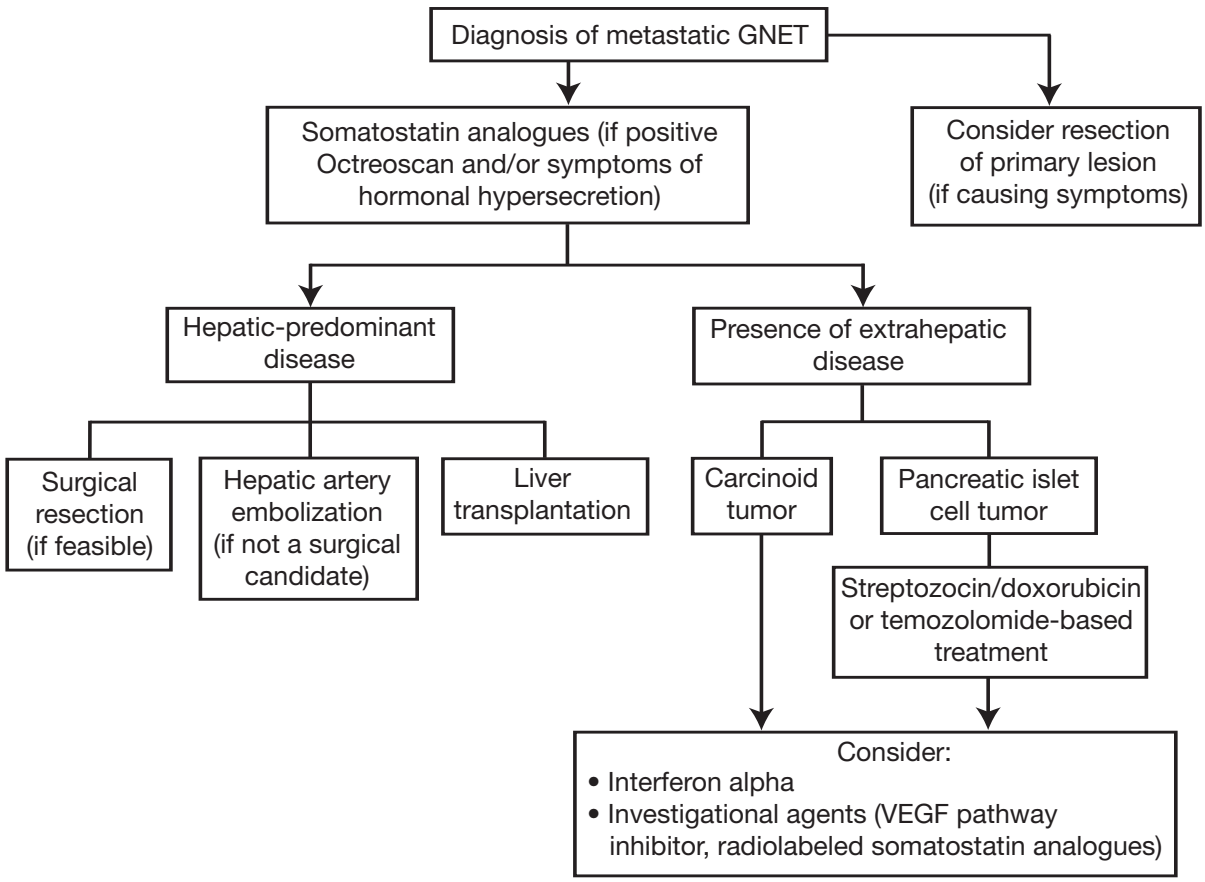

Fig. 7. Treatment algorithm for metastatic gastroenteropancreatic neuroendocrine tumors (GNETs). VEGF, vascular endothelial growth factor.

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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CHAPTER 7

Gastrointestinal Motility Disorders

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G. Richard Locke III, MD

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 intestinal obstruction. 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. In many patients, the role of motility in generating symptoms is unclear. Such patients 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. 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, 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

Abbreviations: ANNA-1, anti-neuronal nuclear autoantibodies type 1; 5-HT, serotonin; TPN, total parenteral nutrition.

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 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 in proximity to 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 (Fig. 1). The fasting (or interdigestive) period is characterized by a cyclic motor phenomenon called the *interdigestive migrating motor complex.* In healthy persons, one cycle of the interdigestive migrating motor complex is completed every 60 to 90 minutes. The interdigestive migrating motor complex has three phases: 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 highest frequency (3 per minute in the stomach and 12 per minute in the upper small intestine). Phase III migrates for a variable distance through the small intestine; there is a gradient in the frequency of contractions from ~12 per minute in the duodenum to ~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: ~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 nitrergic neuron.

Liquids empty from the stomach in an exponential manner (Fig. 2). The half-emptying 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 post-lag 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 (Fig. 2).

PATHOGENESIS OF MOTILITY DISORDERS

Gastrointestinal motility disturbances (Table 1) result from disorders of the extrinsic or enteric nervous system, interstitial cells of Cajal (or intestinal pacemakers), or smooth muscle.

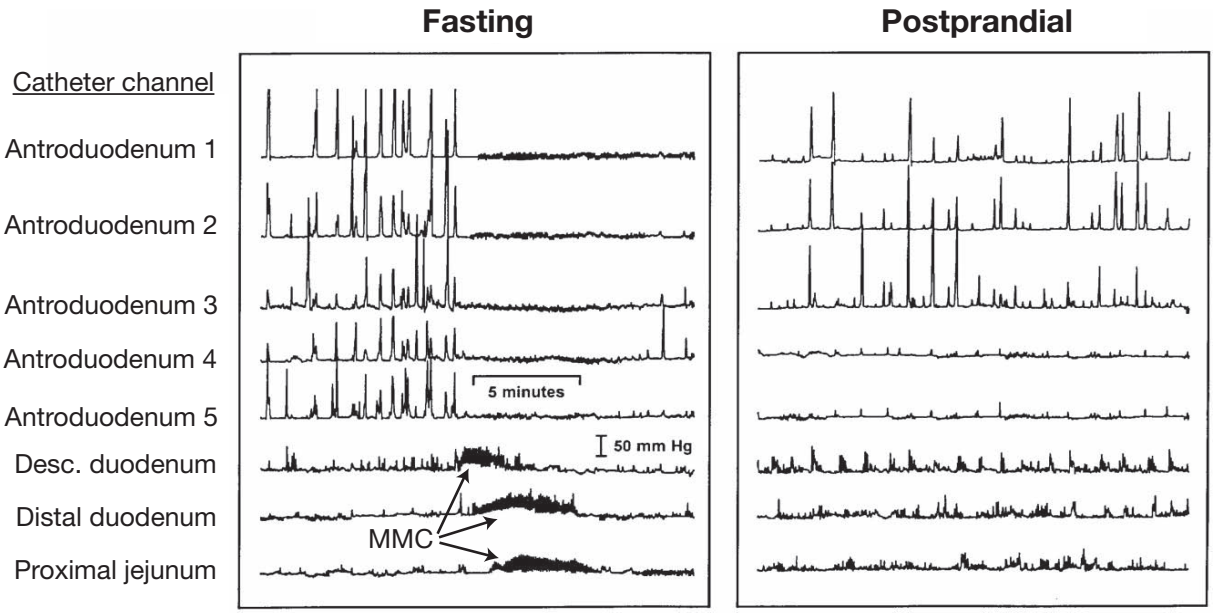

Fig. 1. Fasting and postprandial gastroduodenal manometric recordings in a healthy volunteer. A 535-kcal meal was ingested during the study. Note the cyclic interdigestive migrating motor complex (*MMC*) (*left*) and the sustained, high-amplitude but irregular pressure activity after the meal (*right*). Desc., descending. (From Coulie B, Camilleri M. Intestinal pseudo-obstruction. Annu Rev Med. 1999;50:37-55. Used with permission.)

Combined disorders occur in systemic sclerosis, amyloidosis, and mitochondrial cytopathy and can appear initially with neuropathic patterns; later, with disease progression, they can display myopathic characteristics. Motility disorders can be congenital (affecting the development of the motility apparatus) or acquired.

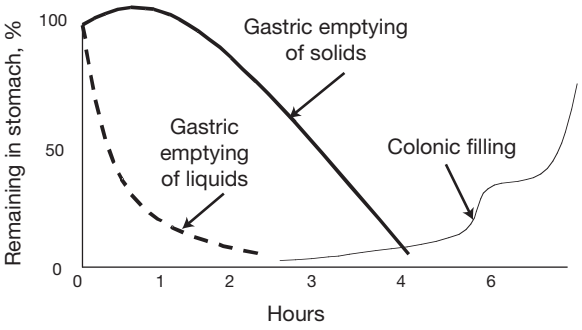

Fig. 2. Schematic representation of typical gastric emptying and colonic filling curves. Note the exponential emptying of liquids, in contrast to the initial retention of solids (lag phase), which is followed by a generally linear post-lag emptying rate. The colonic filling curve is characterized by intermittent bolus transfers.

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), Sox10 (a transcription factor that enhances the maturation of neural precursors), and ckit (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's disease, amyloidosis, and a paraneoplastic syndrome usually associated with small cell carcinoma of the lung. Another common "neuropathic" problem

Table 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's 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 Dopaminergic agents Vincristine Laxatives	
Paraneoplastic	Small cell lung cancer Carcinoid syndrome	
Postoperative	Postvagotomy with or without pyloroplasty/gastric resection	
Endocrine	Diabetes mellitus Hypothyroidism/hyperthyroidism Hypoparathyroidism	

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. However, the latter may occur in patients with a high spinal cord injury or occur secondarily to constipation and fecal impaction. Parkinson's disease and multiple sclerosis are two neurologic diseases involving the extrinsic nervous system that are associated frequently with constipation. In Parkinson's disease, a decrease in the number of dopamine-containing neurons and the presence of Lewy bodies in myenteric plexus neurons have been described. Also, failure of the striated muscles

of the pelvic floor to relax may be an extrapyramidal manifestation of Parkinson's disease. 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 two diseases.

A broad spectrum of gastrointestinal motility disorders may be related to diabetes mellitus: gastroparesis, pylorospasm, intestinal pseudo-obstruction, diarrhea, constipation, and incontinence. All these manifestations may be caused by autonomic dysfunction (Table 2), although evidence points to the importance of acute changes in glycemia and, more importantly, to changes in the structure and function of the enteric nervous system. 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 insulin-dependent diabetes mellitus than in noninsulin-dependent diabetes mellitus and was associated with symptoms of dysautonomia and use of constipating drugs, for example, 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.

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.

Table 2. Gastrointestinal (GI) Manifestations of Diabetes Mellitus

GI manifestation of diabetes	Associated disease	Clinical presentation
↓ Gallbladder motility		Gallstones
Antral hypomotility	Exocrine pancreatic insufficiency	Gastric stasis
Pylorospasm		Bezoars
↓ α_2-Adrenergic tone in enterocytes	Celiac sprue	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 incontinence
Sensory neuropathy		
IAS-sympathetic neuropathy		
EAS-pudendal neuropathy		

EAS, external anal sphincter; IAS, internal anal sphincter; SB, small-bowel.
Modified from Camilleri M. Gastrointestinal problems in diabetes. Endocrinol Metab Clin N Am. 1996;25:361-78. Used with permission.

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. In rare instances, there is a positive family history (eg, hollow visceral myopathy may occur either sporadically or in families). Motility disturbances may be the result of metabolic disorders such as hypothyroidism or hyperparathyroidism, but these patients more often present with constipation.

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 or pneumatosis intestinalis.

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 present 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 affected by the associated mitochondrial neurogastrointestinal encephalomyopathy.

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 in whom stasis and vomiting are important problems 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. Significant 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 in bright lights, absence of sweating, and dry mouth, eyes, or vagina.

A succussion splash detected on physical examination usually is indicative of a region of stasis within the gastrointestinal tract, typically the stomach. The hands and mouth may show signs of Raynaud's phenomenon or scleroderma. Testing

pupillary responses to light and accommodation, testing external ocular movement, and 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's 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. This condition occurs in mentally challenged children (eg, Down's syndrome) but increasingly is recognized in adolescents and adults of normal intelligence. It is treatable with behavioral modification.

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 four 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 is the status of hydration and nutrition?
4. What regions of the digestive tract are affected?

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. Barium 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.
2. Assess gastric and small-bowel motility. After mechanical obstruction and alternative diagnoses such as Crohn's disease have been excluded, a transit profile of the stomach or small bowel (or both) should be performed. Efficiency in the emptying of solids is 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. 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 (Fig. 3). Neuropathies are characterized by contractions of normal amplitude, but abnormal patterns of contractility. In contrast, the predominant disturbance in myopathic disorders is the low amplitude of contractions in the segments affected (Fig. 3).
3. Identify the pathogenesis. Causes of gastroparesis and intestinal pseudo-obstruction are outlined in Table 1. In the absence of a cause for a neuropathic pattern of motor activity in the small intestine, it is necessary to pursue further investigations, including testing for autonomic dysfunction, type 1 anti-neuronal nuclear autoantibodies (ANNA-1) associated with paraneoplastic syndromes, and magnetic resonance imaging of the brain to exclude a brainstem lesion (Fig. 4). Autonomic testing includes 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

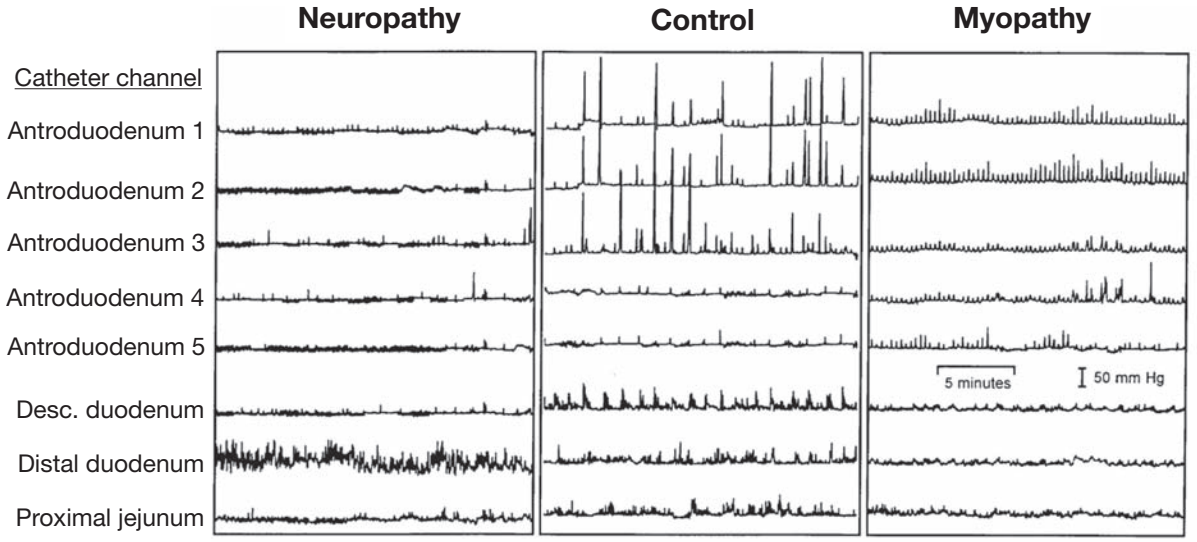

Fig. 3. Postprandial manometric profiles in small-bowel dysmotility due to neuropathy (diabetes mellitus, *left*) and myopathy (systemic sclerosis, *right*). Note the simultaneous, prolonged contractions of low amplitude in myopathy. Although the contraction amplitudes are normal in neuropathy, contractile activity is uncoordinated and contractile frequency is decreased. Desc., descending. (From Coulie B, Camilleri M. Intestinal pseudo-obstruction. Annu Rev Med. 1999;50:37-55. Used with permission.)

testing can identify sympathetic adrenergic or vagal neuropathy. Rarely, brain imaging is indicated for patients with vomiting. 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 (essential element and vitamin levels) and to exclude bacterial overgrowth by culturing small-bowel aspirates. 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 or low-amplitude contractions. Bacterial overgrowth may be difficult to detect with culture of small-bowel aspirates; however, breath hydrogen after a glucose or lactose 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.

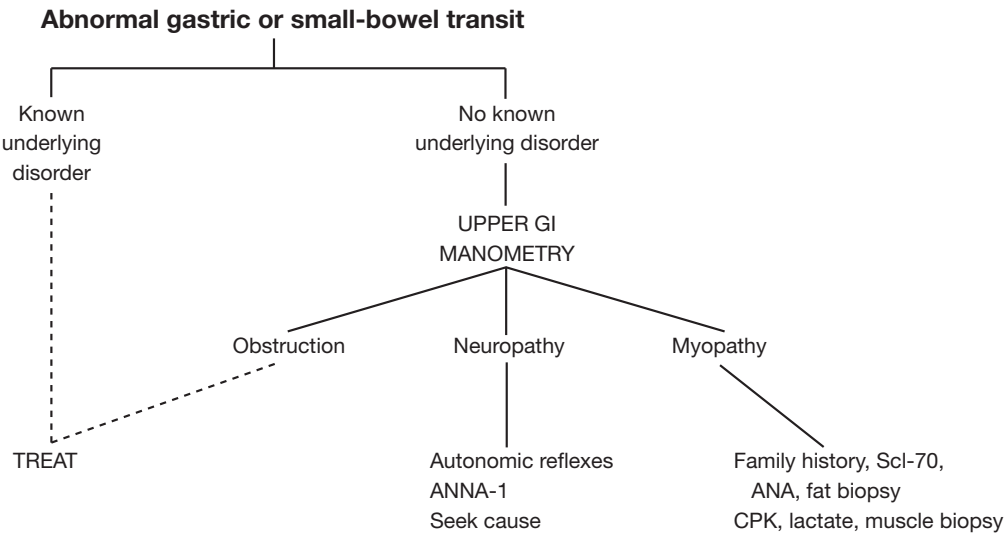

Fig. 4. Flow diagram outlining steps involved in diagnosing gastroparesis and intestinal pseudo-obstruction. ANA, antinuclear antibodies; ANNA-1, anti-neuronal nuclear antibodies type 1; CPK, creatine phosphokinase; GI, gastrointestinal. (Modified from Camilleri M, Prather CM. Gastric motor physiology and motor disorders. In: Feldman M, Sleisenger MH, Scharschmidt BF, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 1. 6th ed. Philadelphia: WB Saunders Company; 1998. p. 572-86. Used with permission.)

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

Medications

Increasingly, medications are being 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 (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 every 8 hours. The effect of oral erythromycin appears to be restricted by tolerance and gastrointestinal side effects, which often prevent treatment for longer than 1 month; sometimes a low dose of liquid formula erythromycin (eg, 40-80 mg 3 times daily before meals) can be tolerated. The elixir formulation may improve absorption in the setting of dysmotility. Although initial 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 anti-5-HT_3 antagonist actions. Long-term use of metoclopramide is limited by the side effects of tremor and Parkinson-like symptoms, a consequence of antidopaminergic activity in the central nervous system. It is available in tablet or elixir form and typically is taken 30 minutes before meals and at bedtime. Usual doses range from 5 to 20 mg 4 times daily.

Serotonergic (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 efficacy in the medium- and long-term; the medication is no longer available for prescription because of the risks of cardiac dysrhythmias (torsades de pointes).

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. Therefore, the therapeutic efficacy of octreotide in intestinal dysmotility associated with gastroparesis and pseudo-obstruction requires further assessment in clinical trials. Currently, octreotide appears to be more useful in the treatment of dumping syndromes associated with accelerated transit. However, it may be used at nighttime to induce activity of the migrating motor complex and to avoid 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, trifluoperazine, and metoclopramide, are important in the management of nausea and vomiting in patients with gastroparesis and intestinal pseudo-obstruction. The more expensive serotonin 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. 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 (two 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 (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.

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 transplantation 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 transplantation is being performed in patients with irreversible TPN-induced liver disease. Complications following small-bowel transplantation include infection, rejection, and lymphoproliferative disorders due to long-term immunosuppression and Epstein-Barr virus infection. Studies have suggested that small-bowel transplantation may improve quality of life and be more cost-effective than long-term TPN. In the future, improvements in immunosuppressive regimens, earlier detection of rejection, and treatment of cytomegalovirus infection based on polymerase chain reaction detection may enable small-bowel transplantation to become the definitive treatment 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 seen 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. Yet, many patients still have symptoms after testing and eradication of *Helicobacter 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 pathogenetic mechanisms have been postulated for functional dyspepsia (Table 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 known. Currently, there is no clear consensus about how best to manage patients who have functional dyspepsia.

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 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

Table 3. Proposed Causes of Functional Dyspepsia

Acid/*Helicobacter pylori*	Motility
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

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, or 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 one in seven) of the adult population has dyspepsia. Not all these people with dyspepsia have functional dyspepsia. In one 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 3. In some ways, thinking about the possible causes has been divided into two camps: acid-*H. pylori* versus motility. This led investigators to try to identify specific symptom subtypes. The idea was that even though the symptoms of dyspepsia could result from multiple causes, refining the symptom criteria would allow more specific causes to be identified. The most recent diagnostic criteria for functional dyspepsia (Rome III) 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 other symptoms such as nausea, fullness, and early satiety. These symptoms suggest that motor abnormalities 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. Metoclopramide may be helpful in part because of its antiemetic effects. Still, long-term treatment with metoclopramide needs to be avoided because of the risk of tardive dyskinesia. Whether a prokinetic efficacious in treating functional dyspepsia will be available in the United States is not clear.

More recently, attention has shifted from gastric emptying to gastric accommodation. 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 nitroglycerin, calcium channel blockers, and

anticholinergics are being evaluated to determine whether they improve the accommodation response. Currently, their effectiveness is not known.

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, how is the clinician to proceed? Current 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 either upper gastrointestinal tract radiography or 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 therapeutic trials of *H. pylori* eradication, proton pump inhibitors, prokinetics, mucosal protectants such as sucralfate, anticholinergics or, finally, low-dose antidepressants. Some patients prefer to consider herbals, hypnosis, or cognitive behavioral psychologic therapy.

Between one-third and one-half of patients with dyspepsia have symptoms that resolve spontaneously. Yet, some are plagued by symptoms long term. It is hoped that newer medications directed at visceral hypersensitivity or gastric accommodation will be useful and strengthen the clinician's armamentarium against this common disorder.

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.

Functional dyspepsia remains a challenge. Currently, emphasis is on the art of medicine and reassurance, limited investigation, treatment trials, and, most importantly, good physician-patient interactions. The hope for the future is that new tests will identify the actual pathophysiologic mechanism, whether in the brain or the gut, that produces the symptoms. This knowledge, in turn, will allow the selection of treatment that will effectively alleviate the patient's symptoms.

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Stomach

Questions and Answers

QUESTIONS

Abbreviations:
CMV, cytomegalovirus
EGD, esophagogastroduodenoscopy
ERCP, endoscopic retrograde cholangiopancreatography
NSAID, nonsteroidal antiinflammatory drug

Multiple Choice (choose the best answer)

1. Which of the following inhibits the production of gastric acid by the parietal cell?

a. Histamine
b. Acetylcholine
c. Prostaglandins
d. Gastrin
e. Lipase

2. Which of the following is not a known mechanism of injury induced by *H. pylori*?

a. Injury to D cells that produce somatostatin, allowing uninhibited gastric acid production
b. Disruption of the function of a mismatch repair gene that, in turn, leads to the development of gastric cancer
c. Production of a protease that thins the mucous layer, leaving the mucosa more prone to injury
d. Inciting the development of autoantibodies that cross-react with gastric epithelial cells
e. Causing lymphoid tissue aggregation that may develop into MALT (mucosa-associated lymphoid tissue) lymphoma

3. What percentage of patients will develop a gastric ulcer (symptomatic or asymptomatic) within the first 3 months of taking nonsteroidal antiinflammatory drugs?

a. 1%
b. 15%
c. 50%
d. 70%
e. 90%

4. Which of the following clinical scenarios may result in a decrease in the serum concentration of gastrin?

a. Taking an H_2-receptor antagonist for 6 months
b. *H. pylori* infection
c. Chronic atrophic gastritis
d. Administration of secretin to a healthy subject
e. Administration of secretin to a patient with Zollinger-Ellison syndrome

5. The overall 5-year survival rate for gastric cancer (all patients) in the United States is:

a. 1%
b. 10%
c. 30%
d. 50%
e. 80%

6. A 65-year-old woman with no history of peptic ulcer disease develops new-onset epigastric pain. EGD shows a 1.5-cm ulcer in the gastric fundus. Which of the following statements is true?

a. The lesion is in an atypical location, and multiple biopsies should be performed
b. If biopsy findings are negative for malignancy, endoscopic ultrasonography should be performed
c. If *H. pylori* infection is found and treated, the patient does not require endoscopic follow-up
d. If *H. pylori* is not seen in biopsy specimens, the patient should be treated empirically for *H. pylori* infection because of the high risk of ulcer recurrence
e. If this ulcer is malignant, it is most likely MALT (mucosa-associated lymphoid tissue) lymphoma

7. The 5-year survival rate for patients with stage I or II gastric lymphoma is:

a. 1%
b. 10%
c. 30%
d. 50%
e. 80%

8. Which of the following statements is true about gastric carcinoids?

a. Gender has no influence on type or prognosis of gastric carcinoids
b. Multifocal gastric carcinoid tumors have a worse prognosis than a solitary gastric carcinoid
c. Prognosis of carcinoid is determined by clinical course more than by stage
d. Carcinoid regression has no relation to serum gastrin levels when the carcinoid is related to Zollinger-Ellison syndrome
e. Gastric carcinoids related to chronic active gastritis typically are aggressive tumors

9. A 62-year-old man is admitted to the hospital with a 1-day history of hematemesis. Recently, he has had fevers and intermittent epigastric pain. He has a history of hypertension, aortic sclerosis, and polymyalgia rheumatica. He does not smoke or drink, and there is no personal or family history of ulcers. His medications include hydrochlorothiazide, a baby aspirin, low-dose prednisone, and omeprazole. His weight is stable. At endoscopy, several 8- to 12-mm ulcers are noted in the body and fundus of his stomach, with some coffee ground material. Which of the following is the most likely explanation for the stomach ulcers in this patient?

a. Lymphoma, B-cell type, secondary to *H. pylori* infection
b. Lymphoma, T-cell type, secondary to celiac disease
c. Benign gastric ulceration
d. CMV ulceration
e. Gastric adenocarcinoma

10. A 42-year-old woman undergoes cholecystectomy, an open procedure, because of dense adhesions from a previous appendectomy. Intraoperative hypotension results in substantial mesenteric ischemia and small-bowel resection. A few days later, diarrhea and hematemesis develop. Bulbar and postbulbar ulcers are found at endoscopy. Which of the following is most likely?

a. She has an increased fasting serum level of gastrin
b. She has a history of peptic ulcer disease
c. She has been given high doses of NSAIDs
d. She has recurrent, further mesenteric ischemia
e. She has CMV enteritis

11. A 19-year-old female model for a shampoo company presents with a several-week history of vague epigastric discomfort, halitosis, early satiety, poor appetite, and a 10-lb weight loss. She is hospitalized and afebrile, with new jaundice. Her serum level of lipase is fourfold normal. Ultrasonography shows mild dilatation of the common bile duct and a normal gallbladder. Abdominal radiography shows a mottled appearance within an enlarged stomach. Which of the following would you recommend?

a. ERCP
b. Cholecystectomy
c. Low fiber diet
d. Conservative therapy
e. Surgery

12. Gastroduodenal manometry is a useful clinical test in which of the situations below?

a. In the evaluation of a patient with scleroderma who has delayed gastric emptying
b. In the evaluation of a patient with suspected rumination syndrome
c. In a patient with unexplained obstructive symptoms (negative small-bowel follow-through) and history of previous abdominal operations
d. In the evaluation of a patient with severe upper gastrointestinal tract symptoms when all other tests are entirely normal
e. In the evaluation of a patient with amyloidosis who has delayed gastric emptying

13. A 16-year-old previously healthy high-school athlete is referred to you because of an 18-month history of daily vomiting, which occurs during and after meals. He has lost 18 lb. The findings of the usual laboratory tests, EGD, computed tomography, abdominal ultrasonography, duodenal biopsies, magnetic resonance imaging of the brain, and adrenal tests were all unremarkable. Which of the following is most likely to be diagnostic?

a. Human immunodeficiency virus testing
b. Additional history
c. Testing for C1 esterase deficiency
d. Porphyrin analysis
e. Esophageal manometry for achalasia

14. Which of the following statements about gastric motility is true?

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

ANSWERS

1. Answer c
Prostaglandins

2. Answer b
Disruption of the function of a mismatch repair gene, that, in turn, leads to the development of gastric cancer

3. Answer b
15%

4. Answer d
Administration of secretin to a healthy subject

5. Answer c
30%

6. Answer a
The lesion is in an atypical location, and multiple biopsies should be performed.

7. Answer e
80%

8. Answer c
Prognosis of carcinoid is determined more by clinical course than by stage.

9. Answer d
This patient, who is receiving immunosuppressive therapy, presents with fever, pain, bleeding, and multiple areas of gastric ulceration. This presentation is very likely to be due to CMV ulceration. B-cell lymphomas due to *H. pylori* infection more often appear as bulkier mass lesions with ulceration or more diffuse, infiltrative maltomas. There is no history of celiac disease, and the associated T-cell lymphomas usually occur in the small bowel. The presentation of gastric adenocarcinoma is unlikely to include multiple ulcerations. Benign stomach ulcers are unlikely in this patient receiving treatment with omeprazole.

10. Answer a
Her presentation with bulbar and postbulbar ulcers, diarrhea, and hematemesis suggests an acid hypersecretory state. Sudden removal of large portions of the small bowel eliminates intestinal-phase inhibitors of gastric acid secretion and can dramatically increase serum levels of gastrin and gastric acid production. Recurrent ischemia several days postoperatively is unlikely, as is CMV infection in an otherwise healthy patient. It is unlikely that she would have received high doses of NSAIDs. Even if she had a history of a previous ulcer, the acute onset, postbulbar ulceration, and diarrhea would not be explained by a previous history of an ulcer.

11. Answer e
The key observation is the mottled appearance within an enlarged stomach seen in an abdominal radiograph. This, plus her early satiety and other symptoms, suggests a bezoar. Vegetable bezoars usually do not interfere with ampullary drainage (jaundice, dilated bile duct, and pancreatitis) but trichobezoars can. A low fiber diet or conservative therapy is unlikely to be helpful. There is no need for cholecystectomy. ERCP could help get hair and material out of the ampullary region, but a large gastric bezoar due to hair requires surgical removal. This patient has Rapunzel's syndrome due to chewing hair, either consciously or unconsciously (while asleep).

12. Answer c
Manometric findings are reasonably specific for mechanical obstruction even when radiographic studies are negative. Patients who have a specific diagnosis that is associated with delayed gastric emptying, such as scleroderma, amyloidosis, or diabetes mellitus, do not need an additional diagnostic test. Rumination is diagnosed on the basis of the history; manometric findings are less sensitive and specific. Gastroduodenal manometry is invasive, not always well tolerated, and unlikely to be helpful in a setting in which other assessments of gastrointestinal function (eg, scintigraphy) are normal.

13. Answer b
Daily vomiting in combination with all the normal test results is peculiar. Additional history shows effortless regurgitation, not vomiting, which often is seen in young stressed persons with eating disorders and weight loss (bulimia or anorexia). Distal esophagitis is not unusual. Psychiatric evaluation and behavioral therapy with diaphragmatic breathing exercises can be helpful. The other tests are not likely to be helpful in this scenario.

14. Answer a
Liquids empty in an *exponential* manner during the fed state, without a lag phase. Triturated solids less than 2 *mm* in diameter are emptied in a linear manner during the fed state, after a lag phase. Indigestible solids smaller than 2 *cm* are emptied during the fasting state by the migrating motor complex, with maximal gastric contraction waves at 3 cycles per *minute*. Objects more than 5 cm in length or larger than 2 cm in diameter will not pass through the pylorus. Delayed gastric emptying is *not* common in functional dyspepsia.

Section III

Small Bowel and Nutrition

CHAPTER 8

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

Amy S. Oxentenko, MD

MALABSORPTIVE DISORDERS AND DIARRHEA

Malabsorption (defect in the mucosal absorption of nutrients) and maldigestion (defect in the hydrolysis of nutrients) both 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 with 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 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 a sodium-dependent active transporter (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 functional) or a decrease in disaccharidases or transport proteins. Carbohydrates that are not absorbed increase the osmolality within the intestinal lumen, which draws more fluid into the lumen in order to maintain an isosmotic state. Colonic bacterial fermentation of these substances increases intestinal gas. The most common clinical syndrome of carbohydrate malabsorption is from lactase deficiency. Congenital lactase deficiency

Abbreviations: EATL, enteropathy-associated T-cell lymphoma; PAS, periodic acid-Schiff; PCR, polymerase chain reaction; SIBO, small intestinal bacterial overgrowth; tTG, tissue-transglutaminase antibody.

Table 1. Mechanisms of Malabsorption

Category	Defect	Cause	Examples
Luminal defect	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/disease
			Drugs (cholestyramine)
		Deconjugation of bile salts	Bacterial overgrowth
Mucosal defect	Diffuse mucosal damage	Diminished surface area, altered absorption/secretion	Celiac disease, tropical sprue, Crohn's disease, Whipple's disease, amyloidosis
	Decreased brush border enzymes	Congenital/acquired deficiency	Lactase, trehalase, sucrase
		Small-bowel damage	Postinfectious lactase
	Transporter defects	Single enzyme defects	Hartnup disease, cystinuria
Delivery defect	Lymphatic derangement	Ectasia of lymphatics	Lymphangiectasia
		Increased lymphatic pressure	Congestive heart failure, 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. Vol 2. 6th ed. Philadelphia: WB Saunders Company; 1998. p. 1501-22.

is present at birth and is rare. Primary lactase deficiency has a delayed onset, and its highest prevalence is 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. 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 and stool pH <6. Quantification of the mucosal enzyme activity of the various disaccharidases is invasive and not widely available. Hydrogen breath tests have replaced oral tolerance tests; an increase in breath hydrogen of 20 parts per million above baseline is indicative of colonic fermentation of the nonabsorbed carbohydrate by bacteria. If the test is positive and the patient has unfavorable clinical symptoms such as bloating or diarrhea, this is indicative of malabsorption with clinical intolerance. False-positive results (small intestinal bacterial overgrowth [SIBO]) and false-negative results (recent treatment with antibiotics or nonhydrogen producers) can occur with breath testing.

Fat Malabsorption

Fat malabsorption is a complex process that requires adequate function of the pancreas, liver,

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 pH 8, it is inactivated in acid overproduction states (eg, Zollinger-Ellison syndrome). 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 the constituents to pass into the enterocyte. At the level of the enterocyte, triglycerides are reesterified and then 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 for absorption, medium-chain triglycerides do not require micellar 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.

The clinical features of fat malabsorption include diarrhea, weight loss, and complications from fat-soluble vitamin deficiencies (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. Quantitation 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/day, but patients with diarrhea from any cause may have up to 14 g/day before it may represent true fat malabsorption. A 72-hour stool collection is optimal, and the patient should be placed on a diet containing 100 g of fat per day several days before stool collection commences.

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/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. Small-bowel abnormalities that lead to fat malabsorption should be evaluated with a combination of small-bowel biopsy, aspiration, and imaging studies. To evaluate for pancreatic causes of fat malabsorption, imaging (computed tomography, magnetic resonance cholangiopancreatography/endoscopic retrograde 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 occur in only a small number of cases. Tests of pancreatic function are not widely available, but they can be performed with secretin (to measure bicarbonate) and cholecystokinin (to measure lipase or trypsin). Alternatively, an empiric trial of pancreatic enzymes can be recommended.

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 1 to 3, with inactivation at a pH >5. When gastric chyme reaches the small intestine, enterokinase from the duodenal enterocyte 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.

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 Table 2.

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 gamma globulins, 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, the patient should receive acid-suppressive therapy before an α_1-antitrypsin clearance test is performed to avoid degradation of α_1-antitrypsin by pepsin.

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. Although dehydration can occur, it is not typical. 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. 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.

Table 2. Causes of Protein-Losing Enteropathies

Nonerosive disease	Erosive disease	Increased lymphatic pressure
Ménétrier's disease	Amyloidosis	Congestive heart failure
Helicobacter pylori gastritis	Inflammatory bowel disease	Constrictive pericarditis
Eosinophilic gastroenteritis	Graft-versus-host disease	Lymphangiectasia (primary vs acquired)
Celiac disease	*Clostridium difficile* colitis	
Small intestinal bacterial overgrowth	Ischemia	Lymphatic obstruction (lymphoma)
		Mesenteric venous thrombosis
Whipple's disease		Retroperitoneal fibrosis
Vasculitides		

Modified from Greenwald DA. Protein-losing gastroenteropathy. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 1. 8th ed. Philadelphia: Saunders Elsevier; 2006. p. 557-64. Used with permission.

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. 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 concentration and the potassium concentration, multiplying by two, and subtracting this amount from 290 mOsm/kg. A gap greater than 100 strongly supports an osmotic cause for the diarrhea, whereas a gap less than 50 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, with lower values indicating urine or water contamination and higher values indicating that the specimen was not processed readily. 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 capacity to absorb the large volume of fluid that it normally does; thus, liters of fluid pass into the colon. 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. Sodium and glucose absorption from the small bowel occurs through a Na-glucose transporter, SGLT-1. Characteristics, common causes, and testing strategies for secretory and osmotic diarrhea are listed in Table 3.

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 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 diarrhea. This diarrhea is treated with cholestyramine, which binds the excess bile salts and improves diarrhea. If more than 100 cm of 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. This can be managed by prescribing a diet that consists of medium-chain triglycerides, which do not require bile salts or micellar 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 is able to assume all the functions of the jejunum. However, the opposite is not true; the jejunum is not able to compensate for the loss of the specialized functions of the ileum. Outcomes of ileal resection include diarrhea (from either an excess of 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 passes into the colon and is excreted in the stool. With a shortened small bowel and absence of the colon, calcium preferentially

Table 3. A Comparison of Osmotic and Secretory Diarrhea

	Diarrhea	
Feature	**Osmotic**	**Secretory**
Stool volume, L/day	<1	>1
Effect of fast on diarrhea	Stops	Continues
Stool osmotic gap	>100	<50
Common causes	Disaccharidase deficiency	Infections/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/ supplementation	Gastrin (not pure secretory)
	Sweeteners/elixirs	Carcinoid syndrome
	Sorbitol	Laxatives (nonosmotic)
	Xylitol	Diabetic diarrhea
	Fructose	Transporter defects/deficiencies
		Chloridorrhea
		Idiopathic
Testing strategies	Dietary review	Stool cultures
	Carbohydrate malabsorption	Structural/mucosal evaluation
	Breath testing	Neuroendocrine hormone levels
	Stool pH <6	Cholestyramine trial
	Avoidance	
	Stool magnesium	

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, free 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's disease or radiation enteritis can result in a functionally shortened bowel, effectively shortening the bowel further without surgical resection. Whether a patient has an intact colon is of considerable importance if the small bowel has been resected. 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.

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 bacterial overgrowth, and because of the disruption of the enterohepatic circulation of bile, bile acid wasting or steatorrhea (or both) develop. 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 bacterial overgrowth, if it is present or suspected.

SMALL-BOWEL DISEASES

Celiac Disease

Celiac disease may occur in genetically susceptible persons 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 1:100. Among symptomatic patients, it is 1:56, and among first-degree relatives of a patient with the disease, it is 1:22. 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 clinical feature(s) 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. Patients who come to clinical attention with celiac disease represent the tip of the "celiac iceberg." Patients with classic celiac disease have features of malabsorption, whereas those with atypical celiac disease tend to have extraintestinal manifestations alone. These "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 4. Patients with silent celiac disease do not have symptoms despite small-bowel biopsy specimens showing the features characteristic of the disease. In these cases, alternative causes of the histologic findings need to be considered. In latent celiac disease, patients have no clinical features and normal small-bowel biopsy findings, but positive serologic findings. No consensus exists about how to manage these patients; however, follow-up with small-bowel biopsies could be considered. The many diseases associated with celiac disease are listed in Table 5.

The three clinically applicable serologic tests for evaluating patients for celiac disease are 1) antigliadin antibodies, 2) endomysial antibodies, and 3) tissue-transglutaminase antibodies (tTG). The IgA-based tTG test is considered the single best test for screening for celiac disease. The anti-gliadin antibody test has less sensitivity and specificity than other serologic markers and is seldom used for evaluation. The various IgA-based serologic studies, including their sensitivity, specificity, and advantages or disadvantages, are listed in Table 6. A serum IgA level is not necessary for first-line screening for celiac disease because of the relatively low prevalence (2%-3%) of IgA deficiency in patients with the disease. In patients with known IgA deficiency, an IgG-based tTG should be performed; the sensitivity and specificity are both nearly 100%. However, this test alone should not be used for first-line screening for the disease in all patients because the sensitivity of the test decreases to approximately 70% in non-IgA–deficient patients. Serologic tests for celiac disease should be considered for 1) patients with typical gastrointestinal manifestations of the disease, 2) patients with atypical manifestations, 3) at-risk groups, and 4) patients who are being followed for their response to a gluten-free diet. For symptomatic patients, however, small-bowel biopsy studies are needed regardless of the results of serologic testing. Also, any positive serologic study needs to be confirmed with a small-bowel biopsy study.

The endoscopic findings in celiac disease include the loss of folds, a mosaic pattern, scalloping, and nodularity. The sensitivity of these endoscopic markers is quite poor; however, if they are seen, small-bowel biopsy specimens should be obtained regardless of the indication for upper endoscopy because of their high yield in showing a pathologic process. Small-bowel biopsy studies are required for the diagnosis of celiac disease, and biopsy studies should be performed in all patients before treatment is initiated. The classic histologic findings include villous atrophy (total or partial),

Table 4. Manifestations of Celiac Disease

	Clinical features	Details
Gastrointestinal	Diarrhea, steatorrhea	
	Flatulence, distention	
	Weight loss, anorexia	
	Abdominal pain	
	Nausea, vomiting	
	Constipation	
	Aphthous stomatitis	
	Angular cheilosis	
Extraintestinal		
Laboratory findings	Anemia	Iron, vitamin B_{12}, folate (may be normocytic, dimorphic)
	Vitamin deficiencies	Vitamins A, D, E, K
	Transaminase levels increased	Hepatic steatosis
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 alkaline phosphatase level
	Enamel defects	Similar to Sjögren's syndrome
	Arthropathy	Nonerosive, polyarticular, symmetrical, large joint
	Muscle cramps/tetany	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

Modified from Farrell RJ, Kelly CP. Diagnosis of celiac sprue. Am J Gastroenterol. 2001;96:3237-46. Used with permission.

crypt hyperplasia, intraepithelial lymphocytosis (>40 intraepithelial lymphocytes per 100 surface enterocytes), and chronic inflammatory cells in the lamina propria (Fig. 1). There is a spectrum of histologic findings in celiac disease, as indicated by the Marsh Classification (Fig. 2). Early Marsh lesions are more likely to produce fewer or no symptoms than late Marsh lesions. An increase in the 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 villous flattening in small-bowel biopsy specimens are listed in Table 7.

Table 5. Disorders Associated With Celiac Disease

Endocrine	Type 1 diabetes mellitus
	Autoimmune thyroiditis
Connective tissue disorders	Sjögren's syndrome
	Rheumatoid arthritis
Immunologic	IgA deficiency
Inflammatory conditions	Inflammatory bowel disease
	Microscopic colitis
Hepatic	Primary biliary cirrhosis
Neurologic	Epilepsy
Renal	IgA mesangial nephropathy
Cardiopulmonary	Carditis
	Fibrosing alveolitis
	Pulmonary hemosiderosis
Other	Down's syndrome

Modified from Farrell RJ, Kelly CP. Diagnosis of celiac sprue. Am J Gastroenterol. 2001;96:3237-46. Used with permission.

These should be considered 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 genetic markers 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, 3) patients who already have been prescribed a gluten-free diet, or 4) patients who are in certain higher risk populations (eg, Down's 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 for some of them. Consultation with a skilled dietician is imperative for patients with celiac disease. Evaluating bone densitometry, determining vitamin and mineral levels and providing replacement therapy, and vaccinating for encapsulated organisms because of functional asplenia should all be considered.

Table 6. IgA-Based Serologic Studies for Celiac Disease

Serologic test	Sensitivity, %	Specificity, %	Features
IgA AGA	85-90	90	ELISA False positive with mucosal damage Replaced in clinical use by other serologic markers
IgA EMA	90.2 (human umbilical cord) or 97.4 (monkey esophagus)	99.6	Immunofluorescence with human umbilical cord or monkey esophagus Subjective, time consuming, expensive
IgA tTG	95.1	98.3	ELISA, human recombinant or RBC-derived, used most frequently Nonsubjective, less expensive Loss of specificity with autoimmunity

AGA, anti-gliadin antibody; ELISA, enzyme-linked immunosorbent assay; EMA, endomysial antibody; RBC, red blood cell; tTG, tissue transglutaminase.

Data from Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology. 2006;131:1981-2002. Used with permission.

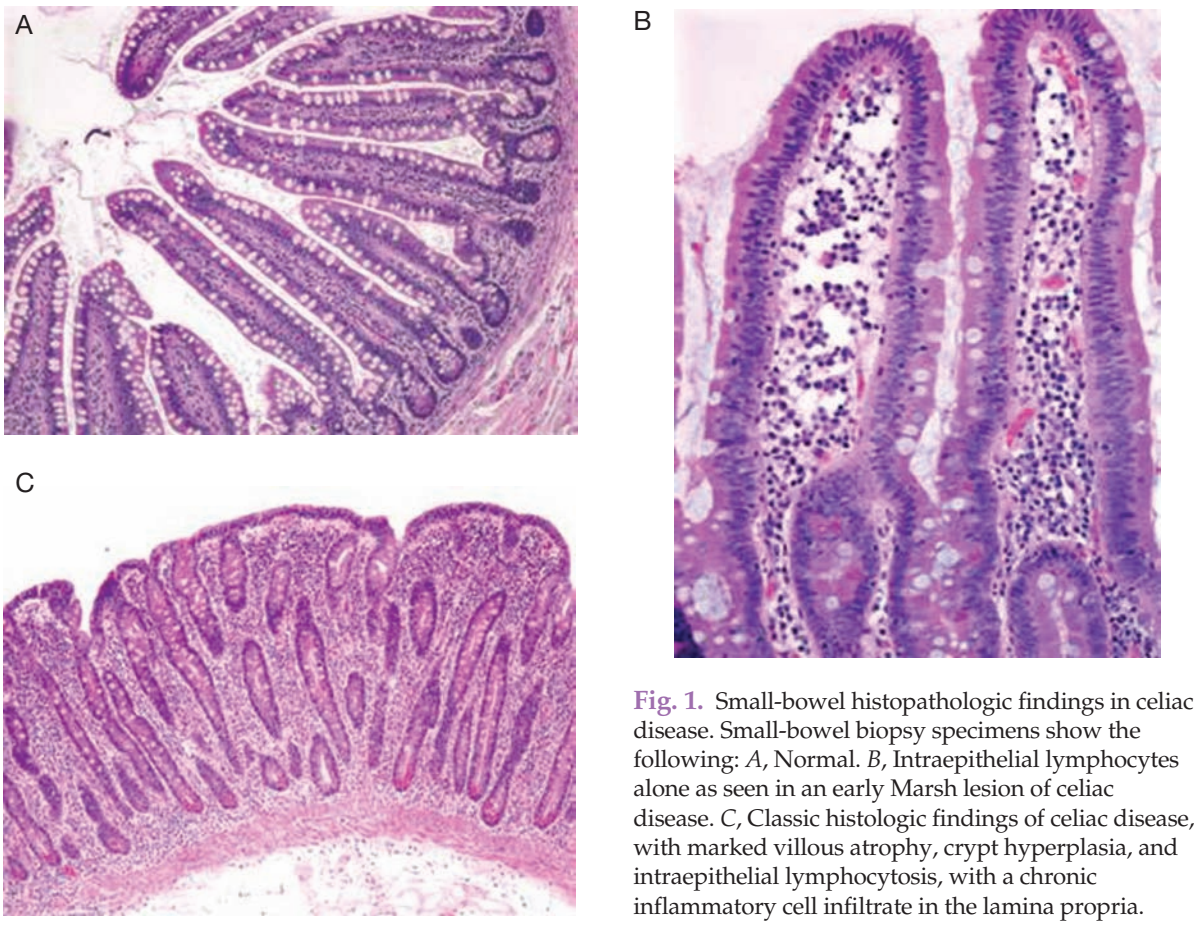

Fig. 1. Small-bowel histopathologic findings in celiac disease. Small-bowel biopsy specimens show the following: *A*, Normal. *B*, Intraepithelial lymphocytes alone as seen in an early Marsh lesion of celiac disease. *C*, Classic histologic findings of celiac disease, with marked villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis, with a chronic inflammatory cell infiltrate in the lamina propria.

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 (Fig. 3). The treatment 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 lesion.

For patients with diagnosed 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? In this instance, the small-bowel biopsy findings 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. Patients with celiac disease are at risk for other conditions that can cause diarrhea, and these should be considered: microscopic colitis, bacterial overgrowth, pancreatic insufficiency, lactase deficiency, and inflammatory bowel disease. Celiac-specific complications also need to be considered, including ulcerative jejunitis, refractory sprue, and malignancy. Imaging or small-bowel biopsy studies (or both) would be required. 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

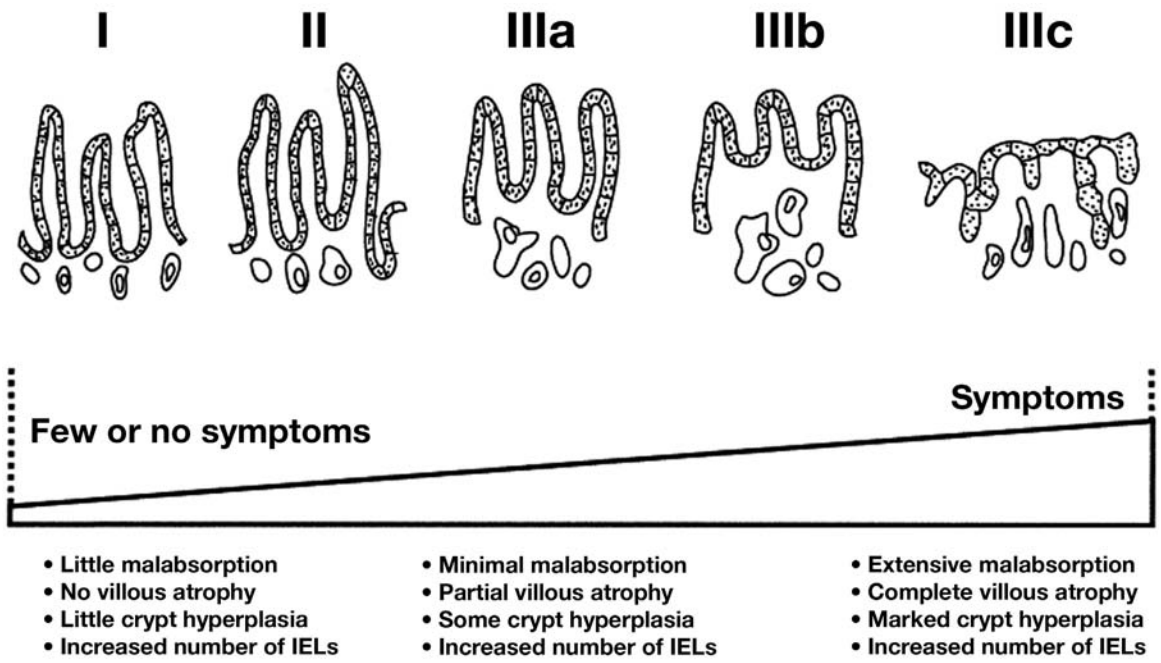

Fig. 2. Marsh classification of the spectrum of histologic findings in celiac disease. IEL, intraepithelial lymphocyte. (From Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology. 2006;131:1981-2002. Used with permission.)

are at increased risk include other forms of non-Hodgkin's lymphoma, small-bowel adenocarcinoma, and oropharyngeal and esophageal cancers.

Table 7. Causes of Small-Bowel Villous Atrophy

Celiac disease
Bacterial overgrowth
Nonsteroidal antiinflammatory drugs
Giardiasis
Crohn's disease
Viral gastroenteritis
Eosinophilic gastroenteritis
Combined variable immunodeficiency
Tropical sprue
Lymphoma
Zollinger-Ellison syndrome
Hypersensitivity to nongluten proteins

Whipple's Disease

Whipple's disease is a multisystem disorder caused by the gram-positive bacillus *Tropheryma whippelii*. This disease usually occurs in white males in the fourth and fifth decades 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 (Fig. 4). This needs to be differentiated from *Mycobacterium avium-intracellulare*, which in addition to being PAS-positive is acid-fast–positive. Electron microscopy can be used to show sickle-shaped *T. whippelii* 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 5. Treatment for

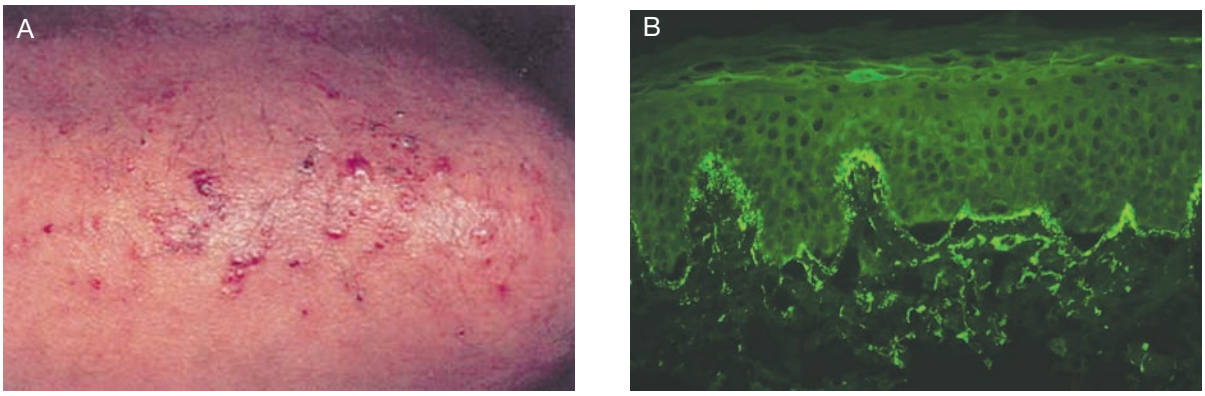

Fig. 3. Dermatitis herpetiformis. *A*, Pruritic papulovesicular rash on the extensor surface of the skin. (From Bennett ML, Jorizzo JL, Sherertz EF. Skin lesions associated with gastrointestinal and liver diseases. In: Yamada T, editor. Textbook of gastroenterology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2003. 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.)

Whipple's disease includes long-term treatment with antibiotics that penetrate the blood-brain barrier. If the patient has pronounced clinical symptoms, penicillin G and streptomycin is often given for 2 weeks intravenously, with trimethoprim-sulfamethoxazole given orally and continued for at least 1 year. Other therapies have had variable success, including doxycycline, hydroxychloroquine, and interferon-based regimens. Disease relapse is not uncommon.

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 at risk, such as Asia, India, the Caribbean, and Central and South America. *Acute tropical sprue* has rapid onset of clinical features and is independent of the length of stay in a tropical area. In comparison, *chronic tropical sprue* has a more steplike presentation and requires 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.

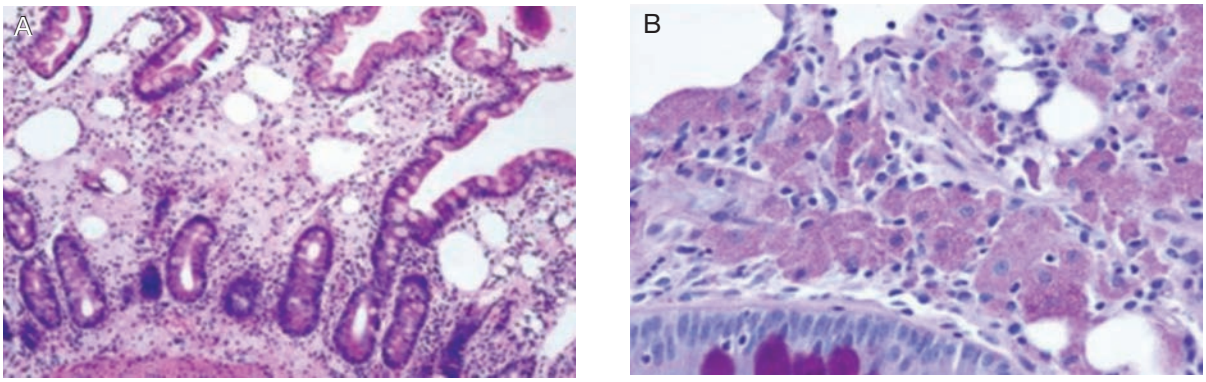

Fig. 4. Histopathologic features of Whipple's disease. Note the widened villi (*A*) filled with foamy macrophages that are periodic acid-Schiff–positive (*B*).

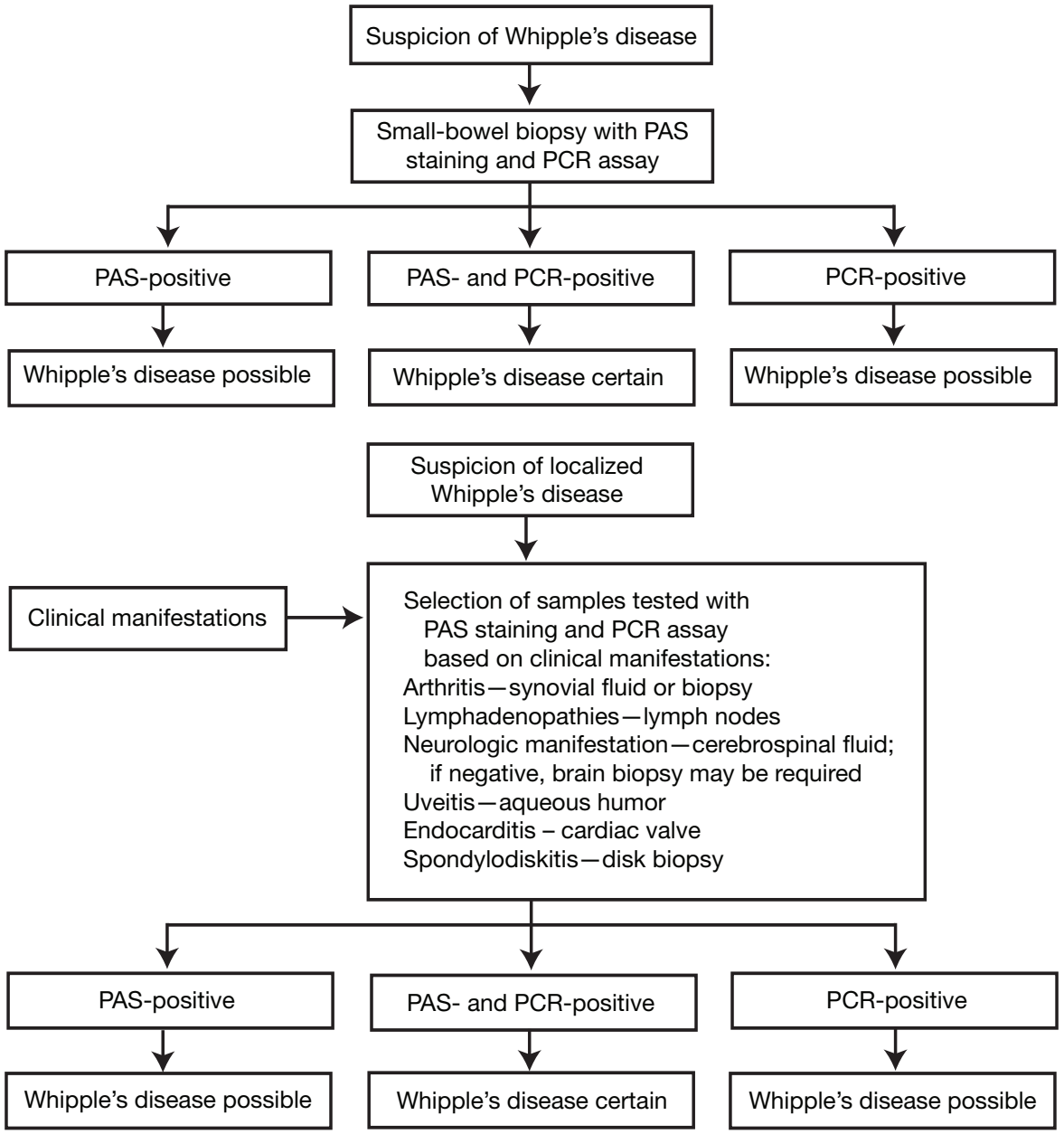

Fig. 5. Strategy for diagnosing Whipple's disease by using periodic acid-Schiff (PAS) staining and the polymerase chain reaction assay (PCR). (From Fenollar F, Puéchal X, Raoult D. Whipple's disease. N Engl J Med. 2007;356:55-66. Used with permission.)

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/day, and vitamin B_{12} replacement produces rapid improvement in the anemia, glossitis, and weight loss of 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

In patients with atopy, 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. Muscular involvement in the submucosa 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. Eosinophilic gastroenteritis needs to be differentiated from hypereosinophilic syndrome which is characterized by a serum eosinophil count greater than 1,500/μL (>1.5 × 10^9/L) for more than 6 months and often has 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.

Intestinal Lymphangiectasia

Intestinal lymphangiectasia occurs as either a primary 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. The secondary form of the disease 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 dilation of the lacteals (Fig. 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.

Treatment for the primary form includes a low fat, high protein diet, with 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 it usually is detected in the submucosa. Amyloid can be deposited also in neuromuscular or 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 small-bowel bacterial overgrowth 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, and they are commonly lactose intolerant. The endoscopic findings in amyloidosis include granularity, friability, and erosions, but often they may be normal. The yield of detecting gastrointestinal

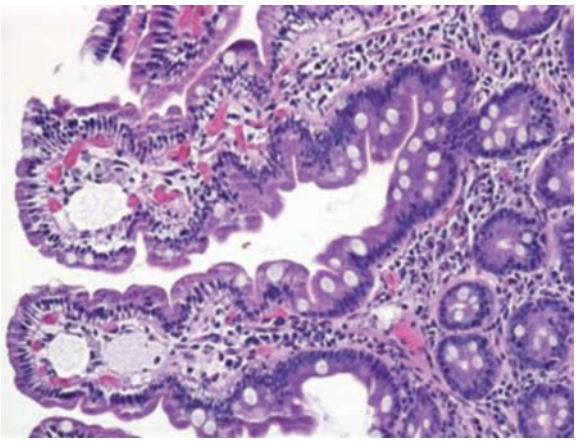

Fig. 6. Lymphangiectasia. Note dilated lacteals in several contiguous villi.

tract involvement by amyloidosis depends on the site from which biopsy samples are obtained, as follows: esophageal 70%, gastric 75% to 95%, small bowel 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 the apple-green birefringence, which is seen best in the walls of the vasculature if the biopsy specimens contain lamina propria. Treatment for involvement of the gastrointestinal tract by amyloidosis includes treating the underlying disease, but treatment for bacterial overgrowth 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, intestinal pseudo-obstruction may occur with systemic scleroderma. In addition, diarrhea may occur from decreased mucosal blood flow due to vasospasm. Treatment of diarrhea in patients with scleroderma includes antibiotics for bacterial overgrowth and a lactose-free diet. 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 are associated with diarrhea, such as metformin and acarbose; 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 bacterial overgrowth. Third, because of the increased prevalence of gluten-sensitive enteropathy among patients with type 1 insulin-dependent 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, patients who have diabetes with end-organ involvement may develop an autonomic neuropathy 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, concentration, and bolus effect of the nutrition), elixir medications (which contain sorbitol), magnesium (as in antacids or replacement/supplementation), intestinal ischemia (especially in critically ill patients), and fecal impaction with secondary overflow. Also, any treatment started with a new medication during hospitalization should be scrutinized as a cause of new diarrhea. Diarrhea that is long standing or present before hospitalization requires evaluation and work-up for chronic diarrhea.

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 resemble colonic flora can overgrow in the small bowel and result in a syndrome of diarrhea and nutritional deficiencies known as *small intestinal bacterial overgrowth* (SIBO).

The many risk factors for SIBO are listed in Table 8, 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 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. Advancing age alone may be a factor. In many patients, no discrete risk factor is identified.

Symptoms of bacterial overgrowth 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 bacteria 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 the 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, there also may be low serum levels of iron, protein, albumin, and fat-soluble vitamins, depending on the degree of malabsorption.

Table 8. Risk Factors for Bacterial Overgrowth

Structural	Small-bowel diverticula
	Intestinal strictures (Crohn's disease, radiation, mediation)
	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
Others	Cirrhosis
	Pancreatitis
	Immunodeficiencies
	Celiac disease
	Age

Modified from Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. Gastroenterol Hepatol. 2007;3:112-22. Used with permission.

The standard for making the diagnosis of SIBO is small-bowel cultures from direct aspiration, 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, and recent antibiotic therapy. 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. An increase of more than 20 parts per million above baseline during the first 90 minutes is indicative of SIBO. 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 (Fig. 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 will be falsely negative in 20% of the population who are nonhydrogen formers. Breath testing results can be affected by recent laxative use, changes in diet, and smoking. Once SIBO is diagnosed on the basis of cultures or breath testing, evaluating for predisposing conditions, for example, with small-bowel imaging, should be considered. Also, an empiric trial of antibiotics could be considered for patients in whom testing for SIBO may not lead to accurate results.

Treatment for SIBO lies in managing the symptoms and replacing the deficiencies. Although modifying the underlying risk factor (tighter glycemic control in diabetes patients, surgery for patients with stricturing disease, and octreotide for patients with scleroderma) that predisposes to SIBO is feasible in only a small fraction of patients, it should be considered. 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 bacterial flora, but rather to decrease and modify the bacterial make-up 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, cephalosporins, fluoroquinolones, 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. Also, lactose avoidance should be considered.

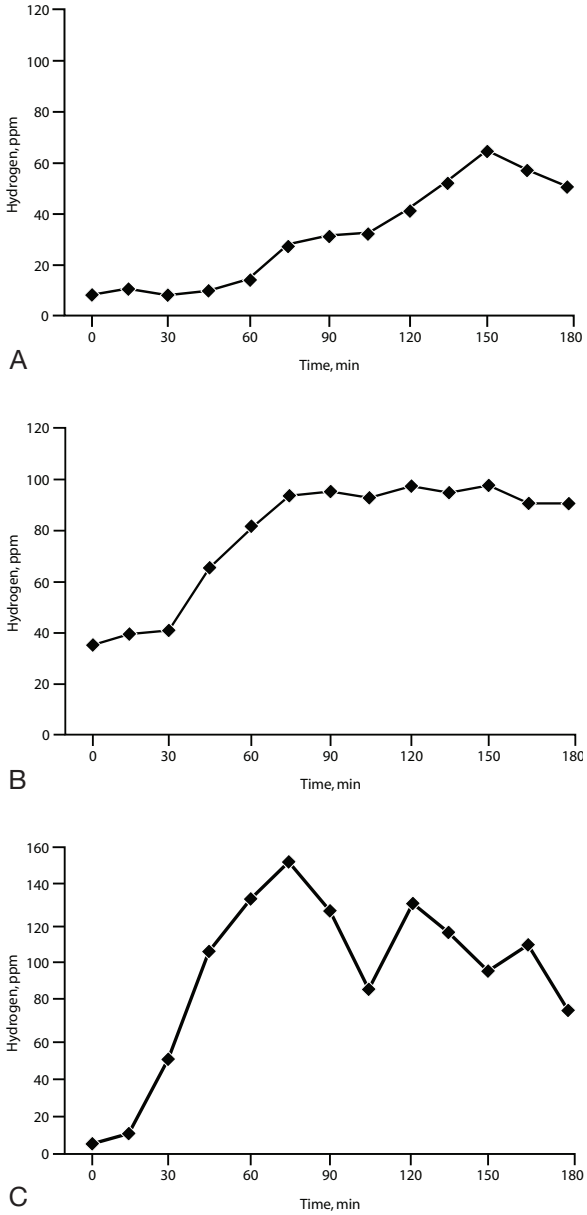

Fig. 7. Breath testing patterns for bacterial overgrowth. *A*, Lactulose breath test without bacterial overgrowth. *B*, Lactulose breath test with bacterial overgrowth. *C*, Lactulose breath test showing double-peak pattern. (From Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. Gastroenterol Hepatol. 2007;3:112-22. Used with permission.)

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CHAPTER 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 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 1 to 2 μg/day, most adults in developed countries ingest 10 to 20 μg/day. 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 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.

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 subacute combined degeneration of the posterior columns of the spinal cord (loss of lower extremity vibratory and sometimes proprioceptive sensation), loss of taste, 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 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 not uncommon 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 absorption (lack of more neutral pH and inactivation of pancreatic proteases) of cobalamin and result in cobalamin deficiency. Vitamin B_{12} deficiency rarely occurs with pancreatic insufficiency itself or with the use of acid-suppressive medications. Bacterial overgrowth, infestation with *Diphyllobothrium latum*, and ileal disease or resection also can result in deficiency of vitamin B_{12}. Often, gastric bypass surgery is complicated by subsequent cobalamin deficiency (lack of intrinsic factor, acid, and gastric grinding function). 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).

Folic Acid

There are many dietary sources of folic acid, including green leafy vegetables, grains, orange juice, and organ meats. Adults should ingest 200 mg/day of folic acid. Brush border membrane hydrolysis of dietary folylpolyglutamates is followed by active transport of folylmonoglutamates, principally in the duodenum and upper jejunum. 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 may occur from folic acid deficiency. Persons with 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, or chronic liver disease are at increased risk for folic acid deficiency.

Other Water-Soluble Vitamins

Vitamin C deficiency results in scurvy, which may include perifollicular hyperkeratotic papules and petechiae; swollen, red, bleeding gums; or anemia. Severe malabsorptive disease and chronic alcoholism increase the risk of vitamin C deficiency. Vitamin C supplementation can increase the risk of adverse cardiovascular events in persons with advanced iron storage disease (hemochromatosis). Supplementation with vitamin C also can produce false-negative results on fecal occult blood tests.

Thiamine (vitamin B_1) deficiency can result in beriberi with cardiac (cardiomyopathy and high-output failure) or neurologic (peripheral neuropathy, cerebellar dysfunction, gaze pareses, or Wernicke-Korsakoff syndrome) disorders, which may be exacerbated by the administration of glucose to thiamine-deficient patients. Chronic alcoholism, long-term renal dialysis, pregnancy, and chronic malnutrition all are risk factors for thiamine deficiency.

Riboflavin (vitamin B_2) deficiency can cause angular stomatitis, cheilosis, glossitis, seborrheic dermatitis, and visual impairment. Chronic alcoholism and malabsorptive disorders are risk factors.

Niacin (vitamin B_3) deficiency due to malabsorptive syndromes, chronic alcoholism, carcinoid syndrome, and isoniazid therapy can produce pellagra (diarrhea, dermatitis, and dementia), glossitis, and angular stomatitis. Excess niacin can cause flushing and hepatocellular injury.

Pyridoxine (vitamin B_6) deficiency can occur in patients treated with isoniazid, cycloserine, hydralazine, oral contraceptives, dopamine, and D-penicillamine. Malabsorptive syndromes and chronic alcoholism also are risk factors. Glossitis, cheilosis, angular stomatitis, seborrheic dermatitis, sideroblastic anemia, and peripheral neuropathy may supervene. Vitamin B_6 deficiency may be responsible for both the only modest increase in aminotransferase values and the increased ratio of aspartate aminotransferase to alanine aminotransferase in alcoholic hepatitis.

Although biotin deficiency is rare, it can occur in patients receiving total parenteral nutrition but not biotin. 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. Lack of vitamin A can produce night blindness, xerophthalmia, a follicular hyper-

keratotic rash, abnormalities of taste and smell, 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 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 (green leafy vegetables) and endogenous (intestinal bacteria) sources. 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 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/day), urinary tract, and skin and menstrual loss in women needs to be matched by iron absorption from the duodenum and upper jejunum. Iron contained in the form of heme from meat is absorbed (up to 25%) more readily 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), as well as ascorbate, reduces inorganic iron from the ferric to the ferrous form. An iron transporter, divalent metal transporter 1, facilitates absorption of ferrous iron. This same transporter also can facilitate the absorption of divalent copper, zinc, and manganese, each of which can compete with and inhibit the absorption of divalent iron. Ferroportin 1 with ferroxidase hephaestin transports iron into the circulation, oxidizes it to the ferric form, and allows it to bind to 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, angular stomatitis, koilonychia, and atrophic lingual papillae. 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) all can contribute to iron deficiency. Iron overload is discussed in Chapter 28, 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. 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 are risk factors for zinc deficiency. 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's disease) can cause copper deficiency.

Copper

Copper deficiency can result in microcytic hypochromic anemia, leukopenia, neutropenia, diarrhea, neurologic disturbances, and bony changes. Clinical conditions in adults that predispose to copper deficiency include total parenteral nutrition without copper supplementation, malabsorptive syndromes, and chronic biliary fistulas. Toxicity from excess administration of oral copper includes acute hemorrhagic gastritis.

Miscellaneous Minerals

Deficiencies of selenium (cardiomyopathy and myositis), chromium (hyperglycemia and neurologic symptoms), manganese (night blindness, tachycardia, tachypnea, headache, and vomiting), or molybdenum (neurologic symptoms) may develop in patients receiving long-term total parenteral nutrition or tube feeding without proper supplementation.

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Small Bowel and Nutrition

Questions and Answers

QUESTIONS

Abbreviations used:
ALT, alanine aminotransferase
AST, aspartate aminotransferase
CT, computed tomography
EGD, esophagogastroduodenoscopy
ICU, intensive care unit
MRI, magnetic resonance imaging
NSAID, nonsteroidal antiinflammatory drug
TPN, total parenteral nutrition
TSH, thyroid-stimulating hormone

Multiple Choice (choose the best answer)

1. A 68-year-old woman is evaluated for abdominal bloating and intermittent diarrhea that has been present for 6 months. The bloating improves after a bowel movement. She has had a 10-lb weight loss during the 6 months. She says she has no other symptoms. There is no history of recent travel, sick contacts, or medication changes. Her medical history is remarkable for pernicious anemia, for which she receives vitamin B_{12} injections monthly. Laboratory studies are notable for iron deficiency anemia, normal level of vitamin B_{12}, and serum level of folic acid >20 µg/L. The TSH level is normal, and tissue transglutaminase antibody is negative. Stool microbiologic findings were negative. EGD shows an atrophic-appearing gastric mucosa. Small-bowel biopsy specimens show increased cellularity in the lamina propria. Colonoscopy, with random biopsy specimens, was negative. HLA testing shows DQ4 and DQ7 positivity. What is the most likely diagnosis?

a. Celiac disease
b. Small intestinal bacterial overgrowth
c. Irritable bowel syndrome
d. Lactose intolerance
e. Giardiasis

2. A 64-year-old man is referred by his primary physician because of abnormalities on recent tests. Within the last week, he had EGD and colonoscopy because of mild iron deficiency anemia. EGD showed multiple small antral erosions. Although the duodenum appeared grossly normal, small-bowel biopsy specimens showed subtotal villous atrophy. Evaluation for *H. pylori* infection was negative. The colonoscopic findings were normal. Tissue transglutaminase antibody was negative. His medical history is unremarkable except for arthritis in the neck, for which he has taken ibuprofen daily for the last few months. He states that he does not have abdominal pain,

diarrhea, or weight loss. Which of the following is the most likely diagnosis?

a. Celiac disease
b. Whipple's disease
c. Crohn's disease
d. NSAID effects
e. Zollinger-Ellison syndrome

3. A 19-year-old woman with celiac disease is evaluated for recurrent symptoms of diarrhea and weight loss. Celiac disease was diagnosed 2 years ago when she presented with similar symptoms. Findings at that time included an increased level of tissue transglutaminase antibody and subtotal villous atrophy and intraepithelial lymphocytosis seen in small-bowel biopsy specimens. She initially had a response to a gluten-free diet, but for the past 3 months, her symptoms have recurred. She states that her diet has not changed. She started college 6 months ago and lives in a dormitory supplied by city water. The initial small-bowel biopsy specimens were reviewed, and the pathologist thinks that the initial diagnosis was correct. Which of the following is the most likely cause of her symptoms?

a. Inadvertent gluten ingestion
b. Microscopic colitis
c. Enteropathy-associated T-cell lymphoma
d. Pancreatic insufficiency
e. Giardiasis

4. A 32-year-old woman with a history of Crohn's disease presents with worsening of her baseline diarrhea. She states that she does not have melena, hematochezia, fevers, or chills. She has mild abdominal cramps, but no localizing pain. She has had a 15-lb weight loss during the last 4 months. She has had extensive small-bowel resections in the past, with approximately 200 cm of small bowel removed. She has been taking the same dose of azathioprine since her last operation 4 months ago, when segments of fibrostenotic bowel were removed. She had taken loperamide intermittently, which was successful in the past, but is no longer helpful. Laboratory findings include a normal complete blood count, C-reactive protein, and TSH. Stool cultures are negative; no fecal leukocytes are noted. No change is seen in the radiographic appearance of the small bowel. Which of the following is most likely to be helpful?

a. Cholestyramine
b. Prednisone
c. Mesalamine
d. Metronidazole
e. Medium-chain triglycerides

5. A 47-year-old woman presents with a 2-year history of diarrhea. She describes her stools as being pale and foul smelling. She has had a 30-lb weight loss over the last 2 years. Physical examination shows a thin female, but the findings are unremarkable otherwise. Laboratory findings include a low serum level of vitamin B_{12}. Because steatorrhea is suspected, a 72-hour fecal fat collection is performed and shows that she excretes 27 g/day of fat. A 5-hour urine collection after ingestion of 25 g of D-xylose discloses excretion of 11 g of D-xylose. Which of the following is most likely?

a. Worsening of symptoms with wheat products
b. A significant alcohol history with recurrent abdominal pain
c. Past history of intestinal resection
d. Known jejunal diverticulosis from scleroderma
e. Family member with recent diagnosis of giardiasis

6. A 67-year-old woman with atrial fibrillation develops sudden, poorly localized abdominal pain and some time later is admitted to the hospital. An abdominal-pelvic CT scan is normal. Angiography demonstrates a large embolus involving the superior mesenteric artery. At surgery, she has an extensive small-bowel resection. By the fifth day postoperatively, she still cannot eat and has significant nasogastric tube output, but otherwise feels well. Which of the following is most likely to help with her nutritional management?

a. Start nasojejunal tube feedings now
b. Increase the dose of her intravenous H_2-blocker

c. Start nasojejunal tube feedings in 5 days
d. Check the serum level of albumin
e. Start TPN

7. A 35-year-old woman with severe Crohn's disease of the terminal ileum, cecum, and ascending colon that is unresponsive to maximal medical therapy presents with chronic, partial, low-grade, distal small-bowel obstruction. She is hospitalized and surgery is planned. TPN was started 1 week ago, before her planned surgery a few days from now. Laboratory tests today show a newly increased ALT level, twice the upper limit of normal. Six days ago she received 2 units of packed red blood cells. Which of the following statements most likely is true?

a. Her husband has chronic hepatitis C virus infection
b. The increased ALT level is due to the TPN
c. The patient has acute posttransfusion hepatitis C virus infection
d. The increased ALT level is due to Crohn's disease
e. The patient has primary sclerosing cholangitis

8. A 26-year-old woman with a long history of Wilson's disease is referred with a 2-month history of an erythematous, scaly rash around her nares and mouth. She is receiving treatment with D-penicillamine as well as pyridoxine. Which of the following is most likely to help her?

a. Begin niacin supplementation
b. Begin medium-chain triglyceride supplementation
c. Begin zinc supplementation
d. Begin vitamin A supplementation
e. Begin riboflavin supplementation

9. A 35-year-old male alcoholic visits his brother who is staying at a Holiday Inn and relates to him his new problems with vision at night. Several months later, the patient's night vision is better but his doctor notes new hepatosplenomegaly, ascites, and hair loss. Which of the following did his brother most likely advise him to take?

a. Zinc, 15 mg/day
b. Vitamin A, 10,000 IU/day
c. Riboflavin, 1.5 mg/day
d. Chromium, 200 μg/day
e. Copper, 2 mg/day

10. A 33-year-old woman with short bowel syndrome after a vascular event has been doing well on TPN for nearly 5 years. Recently, diffuse, persistent myalgias developed. Values for the following are normal: complete blood count, thyroid-stimulating hormone, glucose, creatinine, bilirubin, ALT, and alkaline phosphatase. However, the value for AST is 5 times normal. Which of the following is most likely to be diminished in her blood?

a. Vitamin E
b. Chromium
c. Manganese
d. Selenium
e. Copper

11. A 63-year-old woman presents with anorexia, weight loss, hair loss, and diarrhea. She complains that her food "tastes like garbage." She underwent vagotomy and antrectomy 20 years ago for peptic ulcer disease. She was questioned recently by the police for putting garbage bags onto neighbors' cars. On physical examination, her tongue appears erythematous and shiny. Which of the following is the most likely?

a. Physical examination shows loss of position sense but not vibratory sensation in her arms
b. She has celiac disease
c. The serum homocysteine level is decreased
d. The serum methylmalonic acid level is increased
e. She has pancreatic insufficiency

12. A 52-year-old woman is admitted to the medical ICU with recent onset of confusion. Her family notes that she "drinks a lot of alcohol, eats poorly, and has been bumping into

things." She also has chronic diarrhea and substantial weight loss. On admission, she is alert, disoriented, confused, and quite weak. The blood glucose level is slightly low, and she has mild metabolic acidosis. Findings on CT of the head and abdomen and chest radiography were unremarkable. Vital signs are normal except for mild tachycardia and tachypnea. Which of the following is most important to administer intravenously?

a. Hydrocortisone
b. Glucose
c. Bicarbonate
d. Thyroid hormone
e. Thiamine

13. A 62-year-old male farmer is in the hospital with acute-on-chronic alcoholic pancreatitis. He has just been transferred to the general medical ward from the ICU. Two trials of oral feeding are unsuccessful, with recurrent vomiting. On hospital day 8, a nasojejunal tube is passed and enteral feeding is begun. Congestive heart failure then develops. Which of the following is most likely to explain his subsequent cardiac decompensation?

a. Selenium deficiency
b. Hyperkalemia
c. Hypophosphatemia
d. Volume overload
e. Excess fat in tube feeding

14. A 38-year-old woman with a long history of ileocolonic Crohn's disease, short bowel syndrome after multiple bowel resections, primary sclerosing cholangitis, and home TPN for several years is evaluated because of a resting tremor, muscle rigidity, abnormal gait, and periodic confusion. Which of the following should be done with her TPN?

a. Add more zinc to TPN
b. Discontinue TPN
c. Decrease the total nitrogen content of TPN
d. Remove manganese from TPN
e. Remove copper from TPN

15. A 41-year-old woman presents for evaluation of diarrhea that she has had for 4 months, following a hospitalization for complicated appendicitis. At the time of hospitalization, she presented with right lower quadrant pain and fevers, and a large appendiceal abscess was noted. In addition to removal of the appendix and drainage of the abscess, the last 150 cm of terminal ileum was removed because of fistulous connections to the abscess cavity. She recently underwent takedown of the diverting ileostomy and now has an ileocolonic anastomosis. Which of the following will *not* be malabsorbed?

a. Bile acids
b. Oxalate
c. Vitamin B_{12}
d. Calcium
e. Fat

16. A 46-year-old woman with known celiac disease presents with diarrhea. Since celiac disease was diagnosed, she has followed a strict gluten-free diet and has responded well. However, after 6 months, her diarrhea returned. She states that she has no other symptoms. Her stool frequency is 5 to 6 times daily. Review of her diet shows strict compliance, and the endomysial antibody level is now normal, but initially it was increased. Stool studies show 6 g of fat/24 hours, which has improved from 28 g/24 hours at diagnosis. The best next step in the evaluation should be:

a. Repeat small-bowel biopsy
b. Colonoscopy with biopsy
c. Abdominal CT
d. Small-bowel imaging
e. Quantitative small-bowel culture

17. A 40-year-old man with a history of alcoholism, diarrhea, and flushing is admitted to the hospital. He was found recently to have a positive PPD (purified protein derivative [tuberculin]) and has been receiving treatment with isoniazid. The serum transaminase levels are mildly elevated. A scaly, erythematous,

and hyperpigmented rash is noted on sun-exposed areas of his body. His skin findings are most consistent with which of the following?

a. Niacin deficiency
b. Pyridoxine deficiency
c. Carcinoid syndrome
d. Cutaneous tuberculosis
e. Riboflavin deficiency

18. A 62-year-old woman with chronic primary biliary cirrhosis develops new problems with balance. Loss of proprioception is found on physical examination. She is positive for anti-mitochondrial antibody. The serum bilirubin level is inceased. Which of the following most likely is true?

a. There is heavy metal deposition in the basal ganglia
b. The M1 antibody is positive
c. The serum homocysteine level is diminished
d. The serum vitamin E level is diminished
e. She is vitamin B_{12} deficient

19. A 24-year-old woman from Montana is found to have severe iron deficiency anemia. Multiple stool specimens are guaiac and HemoQuant negative. Which of the following is most likely?

a. She has celiac disease
b. Cameron's ulcerations are found at endoscopy
c. Small-bowel capsule enteroscopy shows multiple angioectatic lesions
d. She has cecal adenocarcinoma
e. She is gravida 5 para 5

ANSWERS

1. Answer b

Gastric acid has the protective effect of limiting bacterial growth in the proximal gastrointestinal tract. Thus, patients with decreased gastric acid or achlorhydria are at risk for small intestinal bacterial overgrowth. This patient has pernicious anemia, which is associated with an autoimmune atrophic gastritis that can lead to achlorhydria. Bacterial overgrowth can cause a low serum level of vitamin B_{12} (in a person who is not receiving replacement therapy) and an increased serum level of folic acid, because folic acid is synthesized by small-bowel bacteria. Achlorhydria also can affect absorption of iron and lead to iron deficiency anemia. Small intestinal bacterial overgrowth can cause histologic changes of subtotal villous atrophy and increased cellularity in the lamina propria, occasionally making it difficult to distinguish this condition from celiac disease. Therefore, the clinical features presented are highly suggestive of small intestinal bacterial overgrowth, and a rotating regimen of antibiotics may be needed to control her symptoms. Because this patient is negative for tissue transglutaminase antibody, has a markedly increased folic acid level, and is not positive for DQ2 or DQ8 (seen in >95% of those with celiac disease), celiac disease is highly unlikely. Although her symptoms may suggest irritable bowel syndrome, this would not account for her weight loss. Patients with bacterial overgrowth may be secondarily lactose intolerant, but this alone would not explain all the clinical or laboratory features. Although giardiasis can cause bloating and diarrhea, the negative stool studies and small-bowel biopsy findings make this diagnosis unlikely.

2. Answer d

This patient's anemia and endoscopic and histologic findings are likely all a consequence of his recent NSAID use. Villous atrophy is not specific for celiac disease. It can occur with NSAID use, giardiasis, bacterial overgrowth, Crohn's disease, immunodeficiency syndromes, lymphoma, and gastrin-producing states such as Zollinger-Ellison syndrome. The paucity of abdominal complaints, the negative tissue transglutaminase antibody, and the lack of other histologic clues (intraepithelial lymphocytes and crypt hyperplasia) make celiac disease less likely. Patients with Whipple's disease may have large-joint arthritis along with gastrointestinal symptoms, but biopsy specimens usually show swollen villi and the lamina propria distended with histiocytes. The endoscopic findings of antral erosions are more likely to be from NSAID use than from inflammatory bowel disease,

especially without other gastrointestinal symptoms. Although Zollinger-Ellison syndrome can cause peptic ulcer disease and villous flattening, it would be quite unlikely without obvious clinical features. This patient's recent NSAID use is much more likely to have caused the aforementioned clinical features.

3. Answer a

In a patient with celiac disease and persistent or recurrent symptoms, the initial step is to review the small-bowel biopsy results with an expert gastrointestinal pathologist to ensure that the diagnosis is well established. After that has been done, it is imperative that the gluten-free diet be reviewed with a trained dietician because approximately one-half of patients with persistent or recurrent symptoms have gluten contamination, either intentionally or inadvertently, in the diet. If the gluten-free diet has been followed, an evaluation for celiac-associated conditions needs to be considered. Although microscopic colitis, enteropathy-associated T-cell lymphoma, and pancreatic insufficiency all need to be considered in a patient with celiac disease who has recurrent symptoms, gluten ingestion would be more likely, especially with the change in the patient's social support and living environment. Infection with *Giardia* could cause the above symptoms, but the patient has no specific risk factors for the infection.

4. Answer e

If a patient has had more than 100 cm of small bowel resected, the usual enterohepatic circulation of bile acids is disrupted, which leads to bile acid deficiency and fat malabsorption. In this case, the patient has had a significant length of small bowel removed, which would put her at risk for bile acid deficiency and fat malabsorption. Her weight loss is supportive evidence of fat malabsorption. In this setting, medium-chain triglycerides can be administered as a source of fatty acids because they are absorbed directly through the intestinal cell membranes. If less than 100 cm is resected, there can be an excess of bile acids and this can act as an irritant in the colon, in which case cholestyramine can be given to bind the excess bile acids. However, cholestyramine would likely worsen this patient's symptoms by binding the remaining bile acids she has. Because none of the laboratory findings provide evidence of active Crohn's disease, it is not clear that prednisone would be of benefit. Similarly, mesalamine would have no role in this case. Metronidazole may be prescribed for patients with irritable bowel disease who have pouchitis or fistulous disease, but it has no purpose in this scenario.

5. Answer b

This patient has significant steatorrhea, as evident by her quantitative fecal fat collection. After steatorrhea has been identified, the evaluation needs to focus on the cause, which most often is a small-bowel or pancreatic source. Although not commonly used, the D-xylose test can distinguish between these two sources. After a 25-g oral load of D-xylose, urine or serum levels can be measured at 1 and 5 hours. For D-xylose to be excreted in the urine, small-bowel and mucosal absorption need to be normal. Detection of D-xylose in the urine (>5 g) suggests that the small-bowel mucosa is intact, pointing to a pancreatic source for the steatorrhea. One of the most common causes of pancreatic steatorrhea is chronic alcoholic pancreatitis, in which case a significant history of alcohol consumption and recurrent abdominal pain would be important clues. Recurrent abdominal pain suggests that the patient may have developed chronic alcoholic pancreatitis. Pancreatic exocrine insufficiency also can cause vitamin B_{12} deficiency because pancreatic enzymes are required to separate R protein from cobalamin so that it may preferentially bind intrinsic factor. All the other choices would lead to abnormalities of the small bowel, which would result in low urinary excretion of D-xylose.

6. Answer e

This patient had an extensive small-bowel resection and 5 days postoperatively still requires nasogastric suction. It is unlikely that the gastrointestinal tract will be ready for any kind of feedings soon. She has been without nutrition for nearly a week, and TPN is indicated. Determining the serum level of albumin is not useful for deciding when and how to feed this patient. It is appropriate that she is receiving intravenous acid-suppressive therapy to avoid acid-induced mucosal injury from the rebound increase in gastric acid secretion that can

occur after resection of large portions of the small bowel (loss of postgastric acid-inhibitory factors). She has no pain or bleeding, and increasing the dose of the H_2-blocker is unlikely to affect nutritional management.

7. Answer b
The ALT level could be increased for all these reasons. Because it is a new increase, it is not likely to be due to either Crohn's disease or her husband's chronic hepatitis C virus infection. The overall risk of her being infected while in a long-term monogamous relationship with her husband is about 5%. Posttransfusion acute hepatitis C virus infection now, and since 1992, in the United States is extremely rare and would not be manifested as an increased ALT level in only 6 days. There is nothing to support the diagnosis of primary sclerosing cholangitis, which is a cholestatic disorder. TPN is the most likely reason for the increased ALT level, either due to overfeeding or as a nonspecific laboratory finding that usually improves over time.

8. Answer c
D-Penicillamine administration can cause pyridoxine deficiency, which is why the patient is taking pyridoxine. Zinc deficiency also can occur from the chelation of zinc. Alopecia, loss of taste sensation, growth retardation, poor wound healing, hypogonadism, diarrhea, and night blindness also can occur with zinc deficiency. D-Penicillamine does not affect riboflavin, which, like pyridoxine, can cause a seborrheic dermatitis. Essential fatty acid deficiency can cause a similar rash, but this patient has no history to suggest such a deficiency, and the essential fatty acids are long-chain, not medium-chain, fatty acids. Niacin deficiency causes a scaly, hyperpigmented rash in sun-exposed areas. This patient has no history to suggest niacin deficiency or vitamin A deficiency.

9. Answer b
Problems with night vision in an alcoholic could be due to vitamin A or zinc deficiency, but not to chromium, copper, or riboflavin deficiency. Vitamin A excess, which is more of a risk in alcoholics taking near-therapeutic or "safe" doses of vitamin A, can result in hepatosplenomegaly, cirrhosis, loss of head and body hair, fever, night sweats, cytopenias, headache, bone pain, proteinuria, and pruritus.

10. Answer d
Selenium deficiency can cause cardiomyopathy or myositis. Vitamin E deficiency causes neurologic dysfunction (posterior columns, brainstem, cranial nerves, and peripheral nerves). Chromium deficiency results in hyperglycemia, neuropathy, and encephalopathy. Copper deficiency can cause microcytic anemia, neutropenia, hypopigmentation, infection, and bone abnormalities. Manganese deficiency (extremely rare, not reported in TPN patients) can cause dermatitis. In persons receiving prolonged TPN, one should be sure that selenium is included.

11. Answer d
This patient most likely has vitamin B_{12} deficiency, given her surgical history, age, and presentation. An erythematous atrophic tongue, anorexia, dysgeusia, neuropsychiatric symptoms, weight loss, and diarrhea are all consistent with this diagnosis. Loss of vibratory sensation occurs before loss of position sense and usually involves the lower extremities. Both the serum methylmalonic acid and serum homocystine levels are increased in persons with vitamin B_{12} deficiency. Celiac disease and pancreatic insufficiency would be unlikely to explain all the findings.

12. Answer e
An alcoholic person with poor nutritional intake is at risk for many vitamin and mineral deficiencies as well as for alcoholic ketoacidosis and hypoglycemia. This patient may well have thiamine deficiency, and it could be fatal to administer glucose before administering thiamine. She is alert and not particularly hypoglycemic. Her mild metabolic acidosis does not require urgent bicarbonate, nor does she immediately need hydrocortisone or thyroid hormone. She may well have Wernicke's syndrome, with confusion, ataxia, and mild high-output heart failure.

13. Answer c
This patient has not been fed adequately for more than a week and most likely is experiencing refeeding syndrome. Hypophosphatemia, as well

as hypokalemia and hypomagnesemia, is often found with this syndrome. The cardiac decompensation is unlikely to be from volume overload alone, and there may be both chronic (malnutrition or thiamine deficiency) and acute (hypophosphatemia) contributing factors. Excess fat in tube feedings is unlikely to be a factor, and selenium deficiency is not likely because of the subacute presentation and lack of history of prolonged TPN without selenium supplementation.

14. Answer d
Manganese accumulation and toxicity can occur with chronic TPN, and the patient presents with parkinsonian-like neurologic symptoms. MRI of the basal ganglia may show abnormality. Patients with chronic cholestasis are at greater risk for manganese toxicity.

15. Answer b
Because this patient has lost more than 100 cm of the terminal ileum, bile acids and vitamin B_{12} are likely to be malabsorbed. With steatorrhea due to inadequate levels of bile acid in the duodenum, calcium is bound to fatty acids and, thus, malabsorbed. Oxalate is overabsorbed by the colon (not bound to calcium, which is unavailable because of its bound state with fatty acids), leading to hyperoxaluria and kidney stones.

16. Answer b
In a patient who has known celiac disease, increased serum antibody levels, and steatorrhea and who has a response to therapy, recurrent symptoms such as diarrhea most often are due to inadvertent (or noncompliance) ingestion of gluten. Because this patient has been compliant and tests to date are normal, she may well have microscopic colitis. All the answers listed are possibilities, but recurrent disease, lymphoma, and bacterial overgrowth are less likely.

17. Answer a
Patients with chronic alcoholism are at risk for pellagra, with dermatitis (as described here) and diarrhea. Exposure to isoniazid binds pyridoxine and decreases the conversion of tryptophan to niacin. Pyridoxine deficiency by itself is unlikely to account for this patient's constellation of findings. Atrophic tongue, angular stomatitis, and cheilitis can be seen with niacin, pyridoxine, or riboflavin deficiency.

18. Answer d
Vitamin E deficiency is rare in adults and usually is seen in association with chronic cholestatic liver disease. Posterior column disease, peripheral neuropathy, hemolysis, retinal damage, and brainstem (ataxia) and cranial nerve damage can occur. This patient is unlikely to have vitamin B_{12} deficiency or a diminished homocysteine level, and the M2, not M1, antibody would be positive. Heavy metal deposition in her basal ganglia from chronic liver disease is unlikely to explain the loss of proprioception.

19. Answer e
New iron deficiency anemia in a young woman is not unusual with multiple pregnancies. Celiac disease is less likely. Blood loss from Cameron's ulcerations would be accompanied by HemoQuant-positive, if not guaiac-positive, stools. Angioectatic lesions with blood loss also would be accompanied by a positive test for occult blood in the stool. Cecal adenocarcinoma would be rare at her age without a positive family history.

Section IV

Miscellaneous Disorders

CHAPTER 10

Gastrointestinal Manifestations of Human Immunodeficiency Virus Infection

Stephen C. Hauser, MD

Nearly 40 million people worldwide have been infected with human immunodeficiency virus (HIV) type 1 and more than 25 million have died. 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 viral load to less than 50 copies/mL and maintenance of adequate CD4 lymphocyte counts (>500/μL [0.5×10^9/L]) 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 counts greater than 200 to 500/μL ($0.2–0.5\times10^9$/L). However, because of cost, compliance, lack of availability of treatment in certain parts of the world, drug resistance, drug toxicity, and drug-drug and drug-alternative substance interactions, not all patients with HIV infection receive adequate therapy. 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 disorders are more likely to be similar to those in non–HIV-infected 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.

Side 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.

Abbreviations: CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HSV, herpes simplex virus.

- Multiple infections often occur simultaneously in immunosuppressed HIV-infected patients.
- Side effects of antiretroviral drug therapy involving the gastrointestinal tract are common.

ORAL CAVITY

Oral lesions are common in HIV-infected patients (up to 80%) and may be the first symptom in up to 10% of patients (Table 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 noncompliant with antiretroviral drug therapy. Thrush is found on physical examination. The CD4 count is 110/μL (0.110×10^9/L), 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 empiric administration of fluconazole.

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, *Candida* is the most common fungal infection and cytomegalovirus (CMV) is the most common viral infection; herpes simplex virus (HSV) infection is less common. *Candida* 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, hence the role of empiric therapy; however, nearly 25% have a second cause of their symptoms (multiple coexistent pathogens). CMV infection and idiopathic esophageal ulceration are unusual if the CD4 count is more than 100/μL (0.1×10^9/L).

Empiric 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/day for 14 to 28 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 (multiple plaquelike, often linear or confluent creamy-white lesions, with bleeding points when removed) is very specific. *Candida* often (up to 50% of cases) is an oral commensal and usually (up to 90% of cases) is found in stool specimens. Also, *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, 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/day) 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, foscarnet, or cidofovir, as well as HAART, usually helps.

HSV esophagitis often presents with multiple small, superficial ulcers ("volcano" ulcers)

Table 1. Oral Lesions in HIV-Infected Patients

Condition	Features	Treatment
Candidiasis (usually *albicans*; non-*albicans* strains may be azole-resistant)	With/without pain: pseudomembranous (thrush), erythematous (atrophic), hyperplastic (painless, white, does not rub off) Culture, KOH, Gram stain, rarely biopsy	Topical nystatin, clotrimazole vs systemic fluconazole, itraconazole
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 Biopsy, viral studies	If symptomatic, high-dose acyclovir or ganciclovir
Herpes simplex virus	Biopsy, Tzanck preparation	Acyclovir, famciclovir, 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 HIV-induced (?)	Topical anesthetics, dexamethasone, systemic corticosteroids, thalidomide
Bacillary angiomatosis	*Bartonella henselae* or *quintana*, papules or ulcers Biopsy	
Syphilis	Rare	
Lymphomatoid granulomatosis	Rare	
Granuloma annulare	Rare	
Mycobacterium avium-intracellulare	Rare	
Non-Hodgkin's lymphoma		
Kaposi's sarcoma		
Squamous cell carcinoma		
Necrotizing gingivitis and periodontitis		

HIV, human immunodeficiency virus.

or erosive esophagitis (Fig. 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 usually is successful. Primary prophylaxis is not recommended. Some patients with frequent, severe recurrences require secondary prophylaxis.

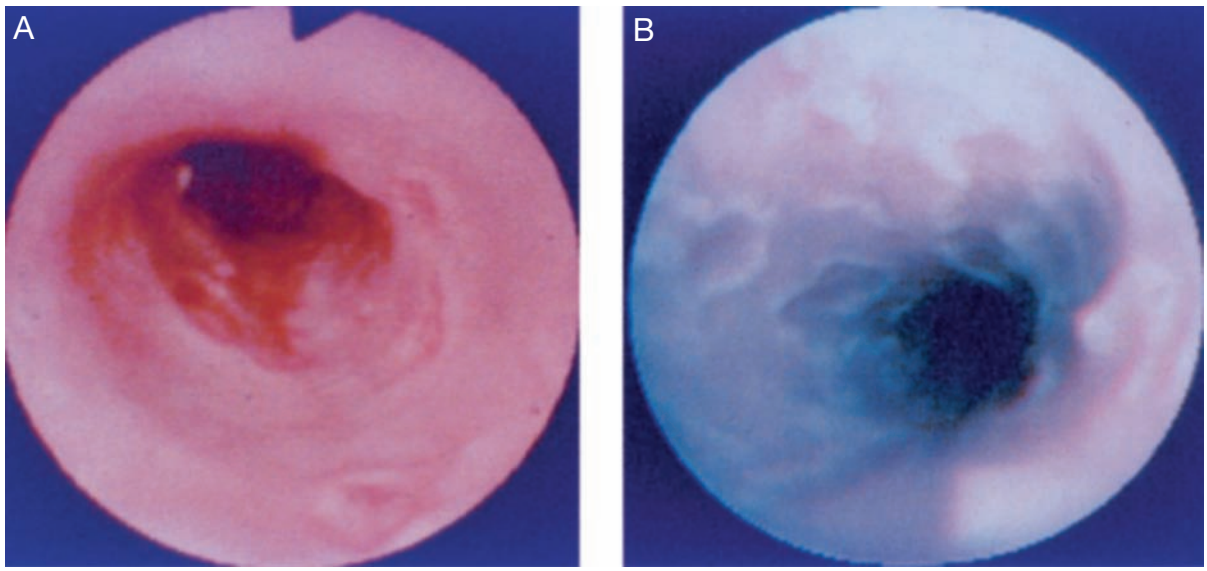

Fig. 1. Endoscopic photograph of herpes simplex esophagitis showing multiple superficial ulcers. *A*, Distal and, *B*, mid esophagus. (From Treadwell TL, Peppercorn MA, Koff RS. The gastroenterology teaching project, unit 6—gastrointestinal infections and AIDS. Used with permission.)

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*, bacillary angiomatosis, *Leishmania*, *Cryptosporidium*, *Pneumocystis*, *Mycobacterium tuberculosis*, and *Mycobacterium avium-intracellulare*, as well as lymphomatoid granulomatosis, non-Hodgkin's lymphoma, and Kaposi's sarcoma.

- *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 or edge of the ulceration, respectively.

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. Gastric lymphoma can present with anorexia, nausea, vomiting, pain, or bleeding, whereas Kaposi's sarcoma involving the stomach is 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, and infection with *M. avium-intracellulare*. Also, idiopathic aphthous ulcers have been identified in the stomach.

SMALL BOWEL

Case—A 35-year-old woman with HIV infection successfully treated with antiretroviral drugs presents with voluminous watery diarrhea after a trip to Haiti. She complains of nausea, cramps, and a recent 5-lb 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 *Isospora 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.

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, lower abdominal pain, and 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 ($0.1–0.2\times10^9$/L). Medications used to treat HIV infection commonly 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, in up to 25% of cases, more than one pathogen may be discovered.

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* (especially if the patient is febrile). If 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 ($>0.2\times10^9$/L) and no pronounced weight loss usually do not have an opportunistic infection and can be given an empiric 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 often include the following: *Cryptosporidium*—This parasite is ubiquitous and transmitted as a zoonosis (humans, cats, dogs, calves, lambs, and other animals, especially newborn pets), by fecal-oral transmission, and, worldwide, through food (raw oysters and unpasteurized juices) and water (including recreational) contamination by as few as 10 to 100 oocysts. It usually infects small-bowel epithelial cells (apical, small [2-8 μm], extracytoplasmic but intracellular sporozoites [Fig. 2]), 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 sensitive than that 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 counts are less than 50/μL ($<0.05\times10^9$/L). 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—Two species of this former parasite now reclassified as a fungus, *Enterocytozoon bieneusi* and *Encephalitozoon* (Septata) *intestinalis*, can be transmitted as a zoonosis or by fecal-oral transmission. Ingestion of watermelon can be a risk factor. *E. bieneusi* involves small-bowel epithelium (small-bowel biopsy, intracellular, 1-2-mm meronts and spores [Fig. 3]) or the hepatobiliary tree. *E. 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 *E. bieneusi* infection. HAART is more likely to be

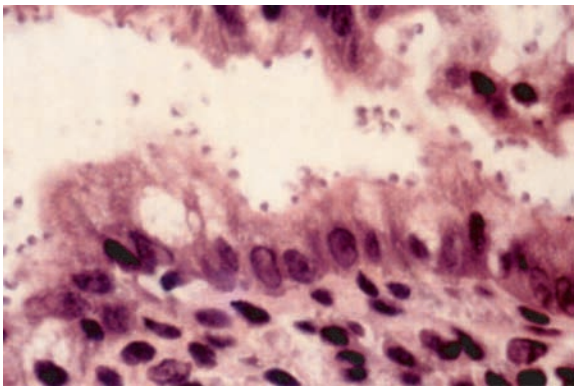

Fig. 2. Jejunal biopsy specimen has apical sporozoites of *Cryptosporidium parvum*. (Hematoxylin-eosin; original magnification, x400.) (From Goodgame RW. Understanding intestinal spore-forming protozoa: *Cryptosporidia*, *Microsporidia*, *Isospora*, and *Cyclospora*. Ann Intern Med. 1996;124:429-41. Used with permission.)

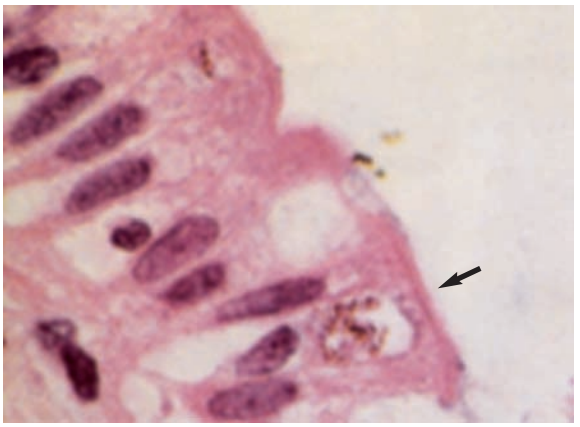

Fig. 3. Small intestinal biopsy specimen has a cluster of microsporidial spores within apical cytoplasm (*arrow*). (Hematoxylin-eosin; original magnification, x350.) (From Case Records of the Massachusetts General Hospital [Case 51-1993]. N Engl J Med. 1993;329:1946-54. Used with permission.)

helpful. The less common *E. intestinalis* infection can be treated with albendazole. *E. intestinalis* may be identified in the lamina propria of the small intestine and in urine sediment.

Isospora—*I. 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. However, recurrences are common in immunosuppressed patients and may require repeat courses of therapy or secondary prophylaxis.

Cyclospora—This parasite is larger than *Cryptosporidium* but smaller than *Isospora*, and the species that infects humans, *Cyclospora cayetanensis*, is transmitted through fecal-oral routes and contaminated water, herbs (Thai basil), and fruit. 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 for *Isospora* infection, trimethoprim-sulfamethoxazole or ciprofloxacin therapy is effective, but relapse may be frequent and require re-treatment or secondary prophylaxis.

Giardia and *Entamoeba*—*Giardia lamblia* and *Entamoeba histolytica* infections are not more common, severe, or prolonged in HIV-infected patients than in non–HIV-infected patients; 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.

Cytomegalovirus—Infection with CMV can occur throughout the gastrointestinal tract but is most common in the esophagus and colon.

Mycobacterium—*M. avium-intracellulare* 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 ($<100/\mu L$ [$<0.1\times10^9/L$]) and often have fever, weight loss, diarrhea, abdominal pain, anemia, and malabsorption. Small-bowel biopsy specimens typically show macrophages stuffed with many acid-fast organisms. Stool and blood cultures also may be diagnostic. Differentiation from *M. tuberculosis*

requires culture results. When present, *M. tuberculosis* 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 (Fig. 4). Multidrug therapeutic regimens improve symptoms, and HAART ultimately can clear this systemic infection.

Other, more uncommon infections that may involve the small intestine include leishmaniasis, toxoplasmosis, *Pneumocystis carinii* (now, *P. jiroveci*) infection, histoplasmosis, candidiasis, coccidioidomycosis, aspergillosis, cryptococcosis, mucormycosis, and strongyloidiasis. Intestinal involvement with Kaposi's sarcoma, often related to human herpesvirus 8 (purplish red submucosal lesions, 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's 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.

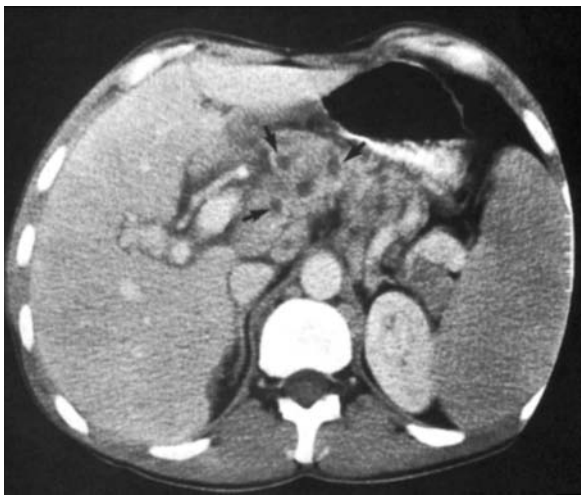

Fig. 4. Abdominal computed tomogram showing punctate areas of central necrosis within enlarged celiac and peripancreatic lymph nodes (*arrows*). (From Jeffrey RB Jr. Abdominal imaging in AIDS. Curr Probl Diagn Radiol. 1988;17:109-17. Used with permission.)

- 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 counts greater than 200/μL, and do not have pronounced weight loss usually do not have opportunistic infections and can be given an empiric 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 young dog and emphasizes the importance of preventing exposure in HIV-infected persons.

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. Blood cultures and stool examination for fecal leukocytes often are positive, especially for *Salmonella enteritidis* and *S. typhimurium*. Other bacterial infections include *Yersinia*; *Aeromonas*; enteroadherent, enteroinvasive, and enteropathogenic *Escherichia coli*; *Vibrio vulnificus* (raw shellfish); and *Listeria*. Exposure to the following should be avoided: reptiles (*Salmonella*); young or sick pets (*Salmonella*, *Campylobacter*, and *Cryptosporidium*); raw or undercooked eggs; meat and shellfish (*Salmonella*, noncholera vibrios, *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). *Streptococcus bovis* sepsis and endocarditis may be associated with gastrointestinal abnormalities such as colon cancer. Empiric treatment with ciprofloxacin may be useful for presumed bacterial infections before the agent is identified. Thus, HIV-infected patients should 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 pâtes, 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 (Fig. 5), mass lesion, perforation, fistula, and weight loss as clinical manifestations. The CD4 lymphocyte counts usually are low (<50-100/µL [<0.05–0.1×10^9/L]). 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.

Clostridium difficile colitis is common, but it is not more severe, persistent, or recurrent in immunosuppressed than in nonimmunosuppressed persons. Other less common infections are due to *M. avium-intracellulare*, *M. tuberculosis*, *Bartonella henselae* (bacillary angiomatosis), *Cryptosporidium*, *E. 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 non-

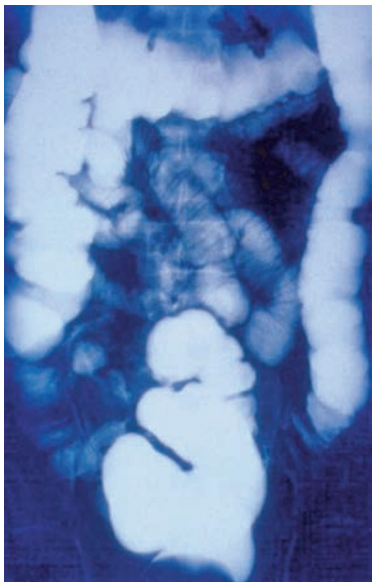

Fig. 5. Barium enema shows cytomegalovirus colitis. Note mucosal edema, ulcerations, and narrowing of the transverse colon. These findings are nonspecific and can occur in other infections as well as in ischemic colitis. (From Treadwell TL, Peppercorn MA, Koff RS. The gastroenterology teaching project, unit 6—gastrointestinal infections and AIDS. Used with permission.)

histolytica Entamoeba, *Balantidium coli*, spirochetes, *Blastocystis hominis*, adenovirus, *Rotavirus*, *Astrovirus*, coronavirus, picobirnavirus, and *Calicivirus*.

Other processes may occur, including lymphoma, Kaposi's sarcoma, toxic megacolon (bacterial infections; CMV, *C. difficile*, or *Cryptosporidium* infections; and Kaposi's sarcoma-related), typhlitis (sometimes without neutropenia), pneumatosis intestinalis (often associated with infections such as CMV, *C. difficile*, *Cryptosporidium*, and *M. avium-intracellulare*), 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 (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* as well as *Actinomyces* infection, Kaposi's 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, dideoxyinosine, pentamidine, dapsone, and trimethoprim-sulfamethoxazole. Infections reported to involve the pancreas are protean and include CMV, *Toxoplasma*, *Pneumocystis*, *Candida*, *Cryptococcus*, histoplasmosis, aspergillosis, *M. avium-intracellulare*, and *M. tuberculosis*. Kaposi's sarcoma and lymphoma also may affect the pancreas.

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CHAPTER 11

Nonvariceal Gastrointestinal Tract Bleeding

Jeffrey A. Alexander, MD

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, but the mortality rate from acute UGI bleeding, ranging from 3% to 10%, has not changed appreciably in the past 50 years. This lack of change in mortality rate likely is related to the increased 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 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 one "baby aspirin" (81 mg) per day.

Initial Approach to Patients With Upper Gastrointestinal Tract 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

Abbreviations: H_2, histamine$_2$; NSAID, nonsteroidal antiinflammatory drug; UGI, upper gastrointestinal.

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 mortality. 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, 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 two most predictive risk factors for mortality. Tachycardia (heart rate >100 beats/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 mortality. 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 mortality. 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 by 72 hours and 98% within 96 hours. The three 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.

Specific Lesions

Peptic Ulcers

The approach to a patient who has bled from peptic ulcer disease is determined at the time of 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 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 three 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 an option in patients with a poor operative risk. 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 >6.0 is required for platelet aggregation and fibrin formation, whereas pH <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/day) or a proton pump inhibitor. Without treatment, recurrent ulcer bleeding will occur in approximately one-third of these patients in 3 to 5 years' time. 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 with H_2-receptor antagonists, proton pump inhibitors, or sucralfate. Although not universally agreed upon, it appears that H_2-receptor antagonists may be slightly more effective than sucralfate. However, they may be associated with a greater incidence of pneumonia and, possibly, mortality. The limited amount of data on proton pump inhibitor therapy for stress ulcer prophylaxis suggests that it is similarly beneficial.

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

This lesion is more frequent in the proximal than 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 third portion. 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. For a patient with an aortic graft, severe bleeding, and negative endoscopic findings, explorative surgery is indicated. 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. Hemosuccus pancreaticus usually represents bleeding 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 (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 (or hereditary hemorrhagic telangiectasias), the elastic tissue disorders of pseudoxanthoma elasticum and Ehlers-Danlos syndrome, CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias) 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.

Dieulafoy's 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. Dieulafoy's 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-UPPER GASTROINTESTINAL TRACT 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 originates from a mid bowel source.

Depending on the transit time, which in turn is determined by the volume of bleeding, patients with non-upper gastrointestinal tract (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 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-colored 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. It is estimated that 3% to 5% of patients with diverticulosis will develop diverticular bleeding. 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 25% of patients. After a second episode, the risk of rebleeding is approximately 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 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 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.

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's Diverticulum

Meckel's 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 radiation 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 for non-UGI bleeding are cytomegalovirus colitis and lymphoma.

NSAID Enteropathy and Colopathy

Increasingly, NSAID enteropathy and colopathy 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. Essential points to keep in mind when answering questions are the following:

- 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 99m-tagged red blood cell radionuclide scans can detect bleeding rates as low as 0.1 mL/minute. 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/minute). Angiographic yields are much greater with active gastrointestinal 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 peranal route (or both), with a diagnostic yield of 50%. Most of the small intestine can be evaluated, and endoscopic therapy can be administered.
- 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.

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CHAPTER 12

Vascular Disorders of the Gastrointestinal Tract

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 (Table 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's syndrome). The stomach, duodenum, and rectum have numerous arterial inputs with rich collateralization. Vascular disorders affecting the stomach, duodenum, or rectum are extremely rare also 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 take-off 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

Table 1. Conditions Predisposing to Secondary Mesenteric Ischemia

Adhesions
Herniation
Volvulus
Intussusception
Mesenteric fibrosis
Retroperitoneal fibrosis
Carcinoid syndrome
Amyloidosis
Malignancy (peritoneal, mesenteric, colonic)
Neurofibromatosis
Trauma

Abbreviation: CT, computed tomography.

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 per 1,000 hospital admissions, with cases distributed equally between the small and large bowel. Risks include age (older than 50 years) and conditions that predispose to stasis, thrombosis, inflammation, or embolism of the mesenteric vasculature (Table 2). Symptoms may be acute (sudden, 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 more severe than the findings on abdominal palpation (ie, pain is much greater than tenderness). Prompt evaluation is critical. Other nonspecific complaints can include fever, nausea, vomiting, abdominal distention, and diarrhea. Physical findings can include abdominal distention, diminished or increased bowel sounds, and nonspecific diffuse abdominal tenderness. Localized abdominal tenderness, rebound, rigidity, altered mental status, and visible gastrointestinal tract bleeding usually are late manifestations of more severe ischemic damage to the small bowel. Occult gastrointestinal bleeding can be an early finding. Leukocytosis with left shift, hemoconcentration, 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, 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 (volume replacement, enhancing cardiac output, diminishing splanchnic vasoconstriction, and administration of broad-spectrum antibiotics). Patients with primary mesenteric

Table 2. Conditions Predisposing to Primary Mesenteric Ischemia

Atherosclerosis or fibromuscular dysplasia
Cholesterol atheromatous embolism
Hypercoagulable or hyperviscosity states
Vasculitis (Fabry's disease, Behçet's syndrome, thromboangiitis obliterans, giant cell arteritis, Takayasu's arteritis, Buerger's disease, Crohn's disease, systemic lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, syphilis, Henoch-Schönlein purpura, dermatomyositis, Köhlmeier-Degos syndrome, Churg-Strauss syndrome, Wegener's granulomatosis, cryoglobulinemia, hypersensitivity vasculitis, Cogan's syndrome, Kawasaki's disease, lymphocytic phlebitis, mesenteric phlebosclerosis)
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

ischemia of the colon (ischemic colitis) usually present with acute abdominal pain (commonly left lower quadrant), often with urgency, diarrhea, and passage of bright red blood per rectum.

INITIAL DIAGNOSTIC EVALUATION

In 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" may be seen. Pneumatosis intestinalis or portal venous gas is a late finding that suggests 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 venous 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, and pneumatosis. 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. 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 peripheral emboli and 50% of cases of primary mesenteric ischemia of the small bowel. The emboli are usually from the heart; an aortic origin is less common. Arrhythmias, cardioversion, cardiac catheterization, myocardial infarction or dyskinesia, congestive heart failure, previous embolism, and age older than 50 years are major risk factors. 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, or anticoagulation (Fig. 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 then restarted 24 to 48 hours postoperatively.

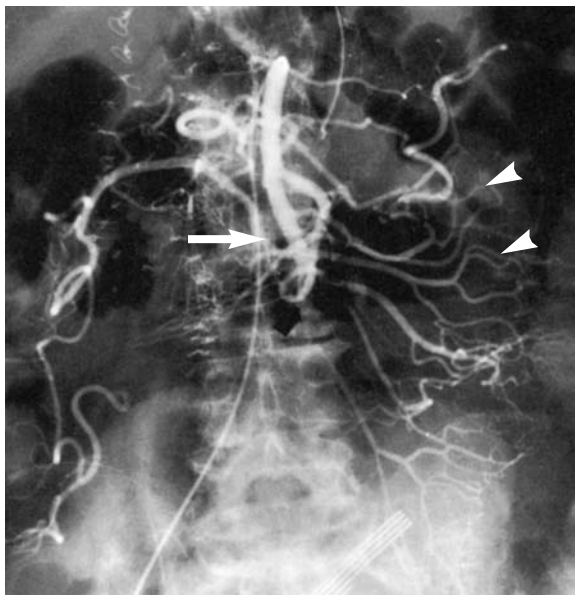

Fig. 1. Anteroposterior view of the aorta showing embolic occlusion of the proximal superior mesenteric artery. Note the normal-appearing proximal jejunal arterial branches (*arrowheads*) and abrupt cutoff (*arrow*) of the superior mesenteric artery. (From McKinsey JF, Gewertz BL. Acute mesenteric ischemia. Surg Clin North Am. 1997;77:307-18. Used with permission.)

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, myocardial infarction, dyskinesia, and congestive heart failure), atherosclerosis (acute-on-chronic ischemia, hypertension, diabetes mellitus, and vasculopathy), hypercoagulable states, vasculitis, and aortic or mesenteric artery aneurysm. Up to one-third of patients have a history of chronic mesenteric ischemia (see below). Therapy usually involves intra-arterial papaverine and surgical thrombectomy or surgical bypass grafting, bowel resection, or some combination of these.

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, or cocaine), and preexisting atherosclerotic disease (hypertension, diabetes mellitus, hyperlipidemia, or vasculopathy). Angiography can be diagnostic (lack of thrombus or embolus, alternating spasm and dilatation ["string-of-sausages" sign], pruning, and spasm of mesenteric arcades) (Fig. 2). 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

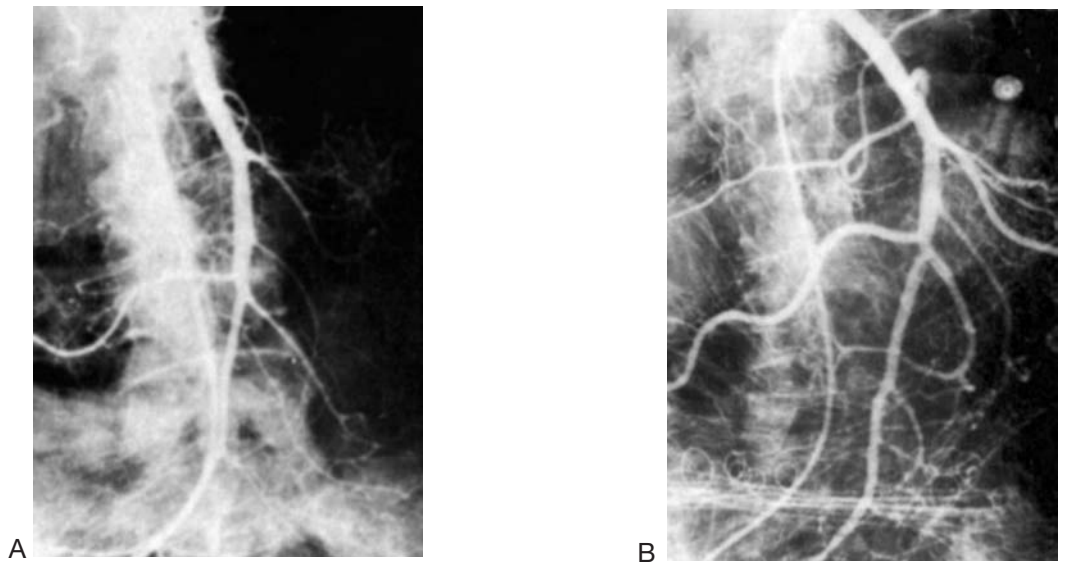

Fig. 2. Patient with nonocclusive mesenteric ischemia before, *A*, and after, *B*, treatment with papaverine. *A*, Angiogram showing spasm of main superior mesenteric artery, origins of its branches, and the intestinal arcades. *B*, Angiogram after 36 hours of papaverine infusion showing that the arteriospasm has resolved. The abdominal symptoms and signs also had resolved. (From Boley SJ, Brandt LJ, Veith FJ. Ischemic disorders of the intestines. Curr Probl Surg. 1978;15[4]:1-85. Used with permission.)

mesenteric ischemia. Risk factors include a personal or family history of hypercoagulopathy and a history of deep venous thrombosis. Causes include hypercoagulable states, hyperviscosity syndromes, intra-abdominal infections (pyelophlebitis) or inflammation, malignant obstruction, portal hypertension, and trauma (Table 3). Symptoms may be acute (hours) or subacute-chronic (days to months) and include abdominal pain (severe, 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 *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 (Fig. 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 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.

Mesenteric venous thrombosis may have the presentation of a subacute or chronic illness, with vague abdominal pain and distention or no symptoms. It may be an incidental CT finding 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.

Table 3. Risk Factors for Mesenteric Venous Thrombosis

Hypercoagulable and hyperviscosity states
Protein S deficiency
Primary myeloproliferative disorder
G20210A factor II gene mutation
C677T MTHFR gene mutation
Antiphospholipid syndrome
G1691 factor V gene mutation
Antithrombin deficiency
Protein C deficiency
Hyperfibrinogenemia
Thrombocytosis
Sickle cell disease
Estrogen or progesterone
Intra-abdominal infections and inflammation
Appendicitis
Diverticulitis
Abscess
Crohn's disease
Pancreatitis
Cholecystitis
Neonatal omphalitis
Portal hypertension
Cirrhosis
Sclerotherapy of varices
Malignant obstruction
Trauma
Vasculitis

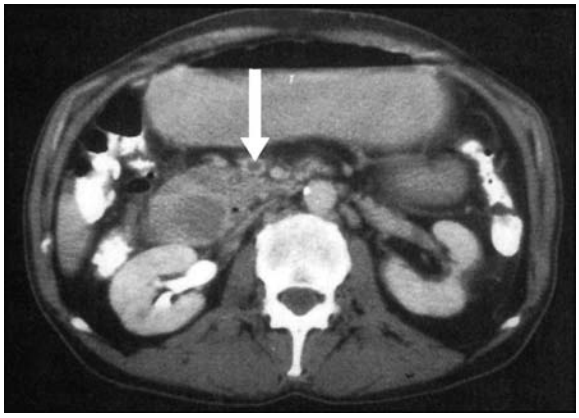

Fig. 3. Abdominal computed tomogram of a patient with acute mesenteric venous thrombosis. *Arrow*, thrombus in the superior mesenteric vein. (From Rhee RY, Gloviczki P. Mesenteric venous thrombosis. Surg Clin North Am. 1997;77:327-38. Used with permission.)

CHRONIC MESENTERIC ISCHEMIA

Patients with classic chronic mesenteric ischemia present with episodic ischemic abdominal pain that typically is postprandial, lasts 1 to 3 hours, and becomes worse with time. Thus, patients lose weight because of fear of eating (sitophobia). Arteriography of these patients usually shows atherosclerotic stenosis of the origin of at least two of the three major visceral arteries. However, this is a common angiographic finding in otherwise healthy age-matched controls. Rarely, the presentation of vasculitis or aortic aneurysm can be chronic mesenteric ischemia. A history of previous vascular disease, hypertension, diabetes mellitus, renal insufficiency, and smoking is common. Nausea, vomiting, diarrhea, constipation, and bloating may occur in addition to abdominal pain and weight loss. 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 on abdominal examination.

Doppler ultrasonography—if able to visualize the celiac and superior mesenteric arteries (each about 80% of cases)—may show increased flow velocities, consistent with marked stenosis. CT angiography and magnetic resonance imaging also may be useful in the identification of proximal large-vessel arterial lesions. However, considering the diagnosis, excluding other causes of abdominal pain and other symptoms (ie, pancreatic cancer, gastric cancer, gastroparesis, small-bowel bacterial overgrowth syndromes, partial small-bowel obstruction, biliary disease, gastric volvulus, or paraesophageal hernias), and obtaining arteriographic results consistent with the clinical findings are crucial. Surgical reconstruction and, in selected cases, angioplasty with or without stents can be therapeutic.

ISCHEMIC COLITIS

Ischemic colitis represents nearly one-half of all cases of mesenteric ischemia. 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, intra-abdominal infections or inflammatory disease, and use of birth control pills, danazol, alosetron, digitalis, vasopressin, gold, pseudoephedrine, psychotropic drugs, ergot, amphetamines, cocaine, or sumatriptan. Often, there is no recognizable cause. Some gastrointestinal infections, such as cytomegalovirus, *Escherichia coli* O157:H7, and *Clostridium difficile* infections, and chronic inflammatory bowel disease can mimic ischemic colitis clinically and histologically. Ischemic colitis due to low-flow states often affects watershed areas such as the splenic flexure, descending colon, and rectosigmoid junction and the right colon. 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 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 one 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, 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 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 is not required, but it may be for patients with more severe ischemic colitis and it should be for patients with

right-sided involvement (which may include the small bowel).

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 should be evaluated for thrombophilic states. Recent studies also lend support to the usefulness of thrombophilic screening in older patients with 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 one 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 (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 take-off 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

Many vasculitic syndromes can involve the gastrointestinal tract. Buerger's disease can cause multiple distal occlusions of medium- and small-sized arteries of the mesenteric circulation. Polyarteritis nodosa typically involves medium- and small-sized vessels, resulting in segmental microaneurysms. Many patients have fever, an increased erythrocyte sedimentation rate, hypertension, and multiple organ involvement. Nearly half are infected with hepatitis B virus. Also, the gallbladder and spleen may be involved. The gastrointestinal tract often is involved in Churg-Strauss syndrome 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 blood vessels. 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 Behçet's syndrome or Wegener's granulomatosis. Mesenteric venous involvement can occur with Churg-Strauss syndrome, systemic lupus erythematosus, Behçet's syndrome, lymphocytic phlebitis, and idiopathic mesenteric phlebosclerosis.

Bowel as well as large-vessel rupture can be a life-threatening complication of Ehlers-Danlos syndrome type IV, 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)—all of which may present with gastrointestinal tract or intraperitoneal hemorrhage.

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CHAPTER 13

Gastrointestinal Manifestations of Systemic Disease

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Many systemic disorders can have gastrointestinal manifestations. This chapter is an overview of these diseases as they affect the gastrointestinal tract and liver, with emphasis on disorders not considered elsewhere in this book.

SYMPTOMS AND SIGNS

Eating Disorders and Weight

Obesity can have adverse effects on the gastrointestinal tract, including an increased risk of symptomatic gastroesophageal reflux disease; increased risk of esophageal, stomach, pancreas, liver, gallbladder, and colorectal adenocarcinoma; increased gallstone formation in women; fatty liver and nonalcoholic steatohepatitis; and complications in obese patients with pancreatitis (gallstones and hypertriglyceridemia). Hypothyroidism, Cushing's syndrome, hypothalamic disorders, Stein-Leventhal syndrome, and drugs (especially antipsychotic agents, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, and glucocorticoids) should be considered in the differential diagnosis of obesity. *Crash diets* with rapid weight loss can result in gallstones (increased cholesterol saturation of bile and decreased gallbladder motility), nausea, vomiting, diarrhea, or severe constipation. Patients with *eating disorders* (eg, bulimia or anorexia nervosa) may present with a wide variety of gastrointestinal problems: nausea, vomiting, gas, abdominal pain, diarrhea, dysphagia, gastroesophageal reflux disease, rumination, Mallory-Weiss tear, gastric dilatation, gastroparesis, constipation, superior mesenteric artery syndrome, cholelithiasis, pancreatitis, increased values on liver function tests, and abnormal gastrointestinal motility.

Nausea and Vomiting

The differential diagnosis is protean and includes drugs (especially narcotics, dopamine agonists, digitalis, chemotherapy, and nonsteroidal antiinflammatory drugs), toxins (alcohol, hypervitaminosis A, and poisoning), infections, vestibular diseases, central nervous system diseases, pregnancy (see below), metabolic disorders (eg, Reye's syndrome, Jamaican vomiting illness, uremia, parathyroid disease, diabetic ketoacidosis, hyperthyroidism, sepsis, and Addison's disease), myocardial infarction (congestive heart failure), and radiation.

Abbreviation: ALA, aminolevulinic acid.

Diarrhea

On occasion, diarrhea can be caused by systemic disorders such as hyperthyroidism, Addison's disease, hypoparathyroidism, collagen vascular diseases, vasculitis, malignancies (eg, carcinoid, gastrinoma, pheochromocytoma, VIPoma, medullary carcinoma of the thyroid, glucagonoma, mastocytosis, and other neuroendocrine tumors), immunologic disorders (see below), amyloidosis (see below), autonomic nervous system disease, diabetes mellitus (see below), and, more commonly, drugs and toxins, including alcohol and radiation.

Constipation

The differential diagnosis should include drugs and toxins, metabolic disorders (hypothyroidism, hypercalcemia, hypokalemia, hypopituitarism, diabetes mellitus, pheochromocytoma, and glucagonoma), neurologic disorders (central, peripheral, or autonomic), myopathies, collagen vascular disease, amyloidosis, porphyria, and pregnancy.

Abdominal Pain

Extra-abdominal causes of acute or intermittent abdominal pain include thoracic disorders (eg, myocardial infarction, pulmonary embolus, pneumonia, and pericarditis), metabolic disorders (diabetic ketoacidosis, diabetic radiculopathy, pheochromocytoma, Addison's disease, uremia, hyperlipidemia, porphyria, angioedema [see below], and hyperparathyroidism), hematologic disorders (sickle cell crisis, hemolysis, and acute leukemia), neurologic diseases (herpes zoster, tabes dorsalis, abdominal epilepsy, and abdominal migraine), drugs, toxins, narcotic withdrawal, aneurysm, and heat stroke.

Jaundice and Abnormal Results of Liver Function Tests

Unconjugated hyperbilirubinemia in the newborn can be caused by hypothyroidism. In adults, *congestive heart failure* is one of the most common causes of mild abnormal results of liver function tests, including mild unconjugated hyperbilirubinemia, mild increases in alanine aminotransferase and aspartate aminotransferase levels, and, less often, a mild increase in the alkaline phosphatase level. Many connective tissue diseases (see below) can be associated with abnormal liver function test results. *Hodgkin's disease* without involvement of the liver or biliary tree, like many infections and sepsis, can be associated with increased alkaline phosphatase levels and even jaundice.

SYSTEMIC DISORDERS

Dermatologic

Many dermatologic disorders can be associated with gastrointestinal vascular bleeding lesions. Hereditary hemorrhagic telangiectasia is an autosomal dominant disorder. Telangiectasias can involve any part of the bowel and the lips, tongue, mouth, extremities, chest, nose, liver, central nervous system, retina, and lung. Endoscopically, these mucosal telangiectasias are indistinguishable from angiodysplastic lesions. Lesions may involve all histologic layers (mucosa to serosa) of the bowel wall. *Blue rubber bleb nevus syndrome*, sometimes autosomal dominant, consists of intestinal and cutaneous cavernous hemangiomas with a bluish, rubbery consistency. Other internal organs also may be involved. Intestinal lesions can result in intussusception. Similar hemangiomas may occur in the sporadic disorder Klippel-Trénaunay-Weber syndrome, involving the gut and skin and hemihypertrophy of a limb and varicose veins. Malignant atrophic papulosis (Degos' disease) consists of painless skin papules with cigarette-paperlike white centers and a telangiectatic periphery and gastrointestinal and central nervous system involvement. All these disorders can cause bleeding and require therapeutic endoscopic or surgical intervention.

Several bullous skin disorders can manifest with involvement of the gastrointestinal tract, including *epidermolysis bullosa* (trauma-induced blisters, oral cavity, esophagus, and anal area, with bullae, webs, strictures, dysphagia, bleeding, and constipation), *pemphigus vulgaris* (oral involvement, esophagus less common, occasionally the lower gastrointestinal tract with bleeding), and *bullous pemphigoid* (oral, less often esophageal or anal involvement). Dilatation (trauma) of strictures in epidermolysis bullosa may lead to more stricturing, and soft diets and corticosteroids may be helpful. Topical or systemic corticosteroids may be useful in treating bullous pemphigoid and pemphigus vulgaris.

Lichen planus can affect the mouth and esophagus (ulcers, strictures, pain, dysphagia; also, an association with hepatitis C virus infection and primary biliary cirrhosis), *psoriasis* can affect the skin and esophagus (webs and dysphagia), and *tylosis* (autosomal dominant) can affect the skin (palmoplantar keratoderma) and esophagus (squamous cell carcinoma; family screening and surveillance endoscopy are indicated).

Immunologic

A host of immunologic disorders have gastrointestinal manifestations. *X-linked (Burton's) hypogammaglobulinemia*, a maturational hereditary defect in B cells, results in gastrointestinal infections (*Campylobacter*, *Giardia*, and rotavirus), small intestinal bacterial overgrowth, and perirectal abscesses. Typically, plasma cells are not seen in rectal biopsy specimens. *Selective IgA deficiency* occurs in about 1 in 500 persons; it is usually sporadic but is sometimes familial. It is associated with a lack of secretory immunoglobulin A1 and A2. Most persons are well, and gastrointestinal infections (*Giardia*) are not common. The prevalence of immunoglobulin A deficiency (1:50) is increased among persons with celiac disease. Other gastrointestinal associations include pernicious anemia, bacterial overgrowth with vitamin B_{12} deficiency, Crohn's disease, and nodular lymphoid hyperplasia. *Common variable (late-onset* or *acquired) hypogammaglobulinemia*, often sporadic, also involves abnormal maturation of B cells, gastrointestinal tract infections (*Giardia* and other parasites, small intestinal bacterial overgrowth, rotavirus, and bacterial diarrhea), malabsorption, pancreatic insufficiency, spruelike disorders, pernicious anemia, gastric cancer, nodular lymphoid hyperplasia, cholelithiasis, autoimmune chronic hepatitis, sclerosing cholangitis, and biliary parasitosis (cryptosporidiosis). Also, carcinoma or lymphoma of the small and large bowel may occur.

Chronic mucocutaneous candidiasis is a heterogeneous group of disorders with defective T-cell function, oropharyngeal or esophageal candidiasis, skin and nail lesions, and various autoimmune (pernicious anemia) and endocrine (hypoadrenal, hypothyroid, hypoparathyroid, and diabetes mellitus) deficiencies. *Hereditary angioedema* is an autosomal dominant (chromosome 11q11-13) disorder with a quantitative or qualitative deficiency of C1 esterase inhibitor, resulting in attacks of nonpitting, painless, nonpruritic angioedema that can involve the skin, mouth, larynx, or gastrointestinal tract. Gastrointestinal tract involvement includes attacks of pain, sometimes with diarrhea, vomiting, intussusception, or transient ascites. Imaging may show edematous bowel. Similar presentations may be due to acquired C1 esterase inhibitor deficiency (collagen vascular diseases and lymphoproliferative disorders). Diagnostic testing includes C1 esterase inhibitor levels (low in 85% of patients), C1 esterase function (low in the 15% with normal or increased inhibitor levels), and C4 levels (absent during attacks and decreased between attacks). C1 levels are normal. Danazol can prevent attacks, and C1 esterase inhibitor concentrate or fresh frozen plasma can be used during attacks. Angiotensin-converting enzyme inhibitors also can cause angioedema of the intestine, independently of diminished complement or C1 esterase inhibitor levels. Angiotensin II receptor antagonists also have been implicated. An estrogen-dependent inherited form of angioedema, also independently of diminished complement or C1 esterase inhibitor levels, has been reported during pregnancy or with the administration of exogenous estrogens.

Cardiovascular

Congestive heart failure can present with liver involvement (hepatomegaly, right upper quadrant pain, mild abnormal results on liver function tests, and ascites with an increased serum-to-ascites albumin gradient) and gastrointestinal involvement (anorexia, nausea, bloating, abdominal pain, diarrhea, malabsorption, protein-losing enteropathy, and low-flow mesenteric ischemia). It is now thought that valvular aortic stenosis might be associated with gastrointestinal angiodysplasia, perhaps on the basis of abnormal von Willebrand multimers. *Cardiac transplantation* may be complicated by an increased risk of bowel perforation, ulcers, cytomegalovirus infection, pancreatitis, and gallstone-related disease.

Pulmonary

α_1-Antitrypsin deficiency can be thought of as either a pulmonary disease with liver manifestations or a liver disorder with pulmonary consequences. Liver disease, including cirrhosis and hepatocellular

carcinoma, is due to the inability of the liver to export an abnormal gene product (usually the ZZ protease inhibitor type, with low serum α_1-antitrypsin levels) and does not occur in the null-null phenotype (no gene product). Patients with *chronic obstructive pulmonary disease* are at increased risk for peptic ulcer disease. Chronic obstructive pulmonary disease and asthma can facilitate gastroesophageal reflux. *Sarcoidosis* is a systemic granulomatous disorder that commonly involves the liver (often asymptomatic, with or without mild increases of alanine aminotransferase, bilirubin, or alkaline phosphatase levels; occasionally progressive hepatic fibrosis resulting in cirrhosis; some patients have severe cholestasis with ductopenia). Less often, sarcoidosis affects the gastrointestinal tract (esophageal involvement with dysphagia, dysmotility, or stricture is rare, often due to hilar or mediastinal lymph node involvement; stomach involvement, with antral ulceration, pyloric stenosis or gastric outlet obstruction, occurs more often; small-bowel disease, with malabsorption or protein-losing enteropathy is rare; colonic involvement is very rare). *Lung transplantation* may be complicated by postoperative colonic perforation and vagal injury, with esophageal and gastric dysmotility, ulcers, pancreatitis, cholelithiasis, and cytomegalovirus infection.

Renal

Chronic renal failure can be complicated by dysgeusia, anorexia, nausea, vomiting, esophagitis, gastritis, angiodysplasias of the gastrointestinal tract, peptic ulcer disease, duodenitis, duodenal pseudomelanosis (asymptomatic), abdominal pain, constipation, pseudo-obstruction, perforated colonic diverticula, small-bowel and colonic ulceration, intussusception, gastrointestinal bleeding, amyloidosis, diarrhea, fecal impaction, and bacterial overgrowth. In patients undergoing *hemodialysis*, a refractory exudative ascites of unclear pathogenesis can develop; this resolves with renal transplantation. These patients also are more at risk for ischemic colitis. Patients who have had *renal transplantation* often develop infections and ulcerative complications of the gastrointestinal tract, diverticulitis, and perforated colonic diverticula. The adult form of *polycystic kidney disease* is associated with hepatic cysts, congenital hepatic fibrosis, and Caroli's disease. (There are rare reports of hyperammonemia and hepatic encephalopathy in patients without previous liver disease who have severe urease-producing *Proteus* or *Escherichia coli* bacterial infections.)

Endocrine

Endocrine disorders commonly affect the gastrointestinal tract and liver. *Diabetes mellitus* can be complicated by disorders of the esophagus (dysmotility, gastroesophageal reflux disease, and candidiasis), stomach (dysmotility, gastroparesis, bezoars, and pernicious anemia), small bowel (dysmotility, bacterial overgrowth, and celiac disease association), colon (dysmotility, constipation, fecal incontinence, and diarrhea), biliary tree (cholelithiasis), pancreas (pancreatic insufficiency), and liver (fatty liver and nonalcoholic steatohepatitis). Diabetic neuropathy and ketoacidosis can present as abdominal pain, and diabetes mellitus is a risk factor for several forms of primary mesenteric ischemia. *Acromegaly* is associated with an enlarged tongue, an increased risk of colonic adenomas (which may be large, multiple, and right-sided), colon cancer, and, perhaps, stomach cancer. Gallstones are a risk in patients receiving octreotide therapy. Patients with *Addison's disease* may present with anorexia, nausea, vomiting, weight loss, malabsorption, abdominal pain, and diarrhea. Also, the disease may be associated with atrophic gastritis and pernicious anemia. Serum levels of aminotransferase levels may be increased. *Hypercortisolism* may be associated with gastric ulceration and increased aminotransferase levels. Pheochromocytoma may occur with hypertension, abdominal pain, ischemic colitis, and diarrhea or ileus. *Hyperthyroidism* may manifest as hyperphagia, weight loss, mild diarrhea, steatorrhea, abdominal pain, vomiting, concomitant atrophic gastritis, dysphagia, ascites, jaundice, and nonspecific mild abnormalities in liver function test results. Autoimmune chronic 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 protein). Associated gastrointestinal diseases include pernicious anemia, ulcerative colitis, primary biliary cirrhosis,

autoimmune chronic hepatitis, and celiac 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.

Hematologic

Sickle cell anemia often results in severe abdominal pain with sickle cell crisis. The liver also may be affected, with pain (congestion and infarction), fever, and increased values on liver function tests. As in other hemolytic states, cholelithiasis (black pigment stones) is common. *Hemolytic uremic syndrome* and *thrombotic thrombocytopenic purpura* can be complicated by gastrointestinal tract bleeding, ulceration, perforation, toxic megacolon, cholecystitis, and pancreatitis, and often they are associated with gram-negative infections, such as those caused by *E. coli* O157:H7, *Shigella*, *Salmonella*, *Yersinia*, and *Campylobacter*. A host of *hypercoagulable states*, some caused by hematologic malignancies, have been implicated in cases of Budd-Chiari syndrome, portal venous thrombosis, and primary mesenteric (venous and arterial) ischemic states. *Hypocoagulable states*, such as hemophilia, and platelet abnormalities often result in gastrointestinal tract bleeding, obstruction, intramural hematomas, or intussusception. Bone marrow transplantation frequently is complicated by acute graft-versus-host disease, with gastrointestinal (nausea, vomiting, and diarrhea; epithelial cell apoptosis seen in biopsy specimens), liver (abnormal liver function tests), and skin abnormalities. Sinusoidal obstruction syndrome (veno-occlusive disease) usually develops before day 20 after transplantation with hepatomegaly, jaundice, and weight gain. Chronic graft-versus-host disease may include severe cholestatic liver disease and esophageal webs and strictures.

Four of the *porphyrias* can occur with acute abdominal crises (abdominal pain, vomiting, constipation, and hyponatremia are common). These four are acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and aminolevulinic acid (ALA) dehydratase deficiency. The first three are autosomal dominant. *Acute intermittent porphyria* is the most common acute porphyria. It 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*, only the ALA level is increased; there are no skin findings, and the condition is autosomal recessive. Abdominal crises may be precipitated by fasting, medications, alcohol, intercurrent illnesses, and menstruation. Urine ALA and porphobilinogen levels (ALA only with ALA dehydratase) are always increased during an acute abdominal crisis. In acute intermittent porphyria, urinary ALA and porphobilinogen values usually are increased between attacks. *Porphyria cutanea tarda* affects only the skin and is associated with alcohol abuse or alcoholic liver disease, mild iron overload or hemochromatosis, and hepatitis B or C virus infection. *Erythropoietic protoporphyria*, with skin manifestations, can result in cirrhosis and liver failure due to hepatic deposition of protoporphyrin.

Mastocytosis is a systemic infiltrative disorder of bone marrow, skin, bone, spleen, the central nervous system, the gastrointestinal tract, and the liver. Periodic flushing (precipitated by alcohol, stress, heat, or medications), hypotension, urticaria pigmentosa, Darier's sign (urticaria after scratching), chest pain, dyspnea, abdominal pain, vomiting, diarrhea, and paresthesias may occur. Malabsorption, peptic ulcer disease (gastric acid hypersecretion), complicated gastroesophageal reflux disease, hepatomegaly, splenomegaly, increased serum alkaline phosphatase value, and, rarely, portal hypertension and hepatic fibrosis may occur.

Oncologic

Leukemias and *lymphomas* commonly involve the gastrointestinal tract and liver. Hodgkin's 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 α *chain disease* (immunoproliferative small intestine disease), which diffusely infiltrates the small bowel

and adjacent lymph nodes (B cells, α heavy chains produced in excess); *mantle cell lymphomas*, which mimic a multiple polyposis syndrome; *multiple myeloma* or *amyloidosis*, with focal plasmacytomas (mass, ulceration, bleeding, or obstruction), gastrointestinal mucosal infiltration with malabsorption, or hyperviscosity syndrome (ischemia); *Waldenström's macroglobulinemia*, with gastrointestinal and hepatosplenic infiltration and malabsorption; and *small cell carcinoma of the lung* and other malignancies, with paraneoplastic pseudo-obstruction (patients may be positive for anti-neuronal nuclear antibody, type I Purkinje cell antibody, or N-type calcium channel-binding antibody).

Bone marrow transplantation often is complicated by *graft-versus-host disease*. Acute graft-versus-host disease with rashes, small and large intestinal mucosal involvement (diarrhea, protein-losing enteropathy, malabsorption, pain, bleeding, and apoptotic bodies seen in biopsy specimens, even in endoscopically normal-appearing areas), and cholestatic liver disease usually occurs in the first 100 days after transplantation. Chronic graft-versus-host disease with cholestatic liver disease (vanishing bile ducts), esophageal disease (dysphagia, strictures, and webs), skin disease, and polyserositis usually occurs after 100 days. *Veno-occlusive disease of the liver*, with bland, nonthrombotic obliteration of small hepatic veins and venules due to conditioning (radiation or chemotherapy) therapy, usually occurs 8 to 23 days after transplantation.

Neuromuscular

Many neurologic and muscular disorders affect the gastrointestinal 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 in this setting, apparently as a result of vagal stimulation of gastrin and gastric acid production. Similar ulceration can occur after body burns covering a large surface area. Abdominal pain, nausea, and vomiting rarely are attributed to *migraine* or temporal lobe *epilepsy*, the latter often including central nervous system symptoms. Cyclic vomiting may present with recurrent attacks of abdominal pain, nausea, and vomiting. *Cerebrovascular disease* and *cerebral palsy* commonly result in oropharyngeal dysphagia due to dysmotility. *Multiple sclerosis* frequently affects the gastrointestinal tract with oropharyngeal dysphagia, gastroparesis, constipation, or disorders of defecation or fecal incontinence. Patients with *Parkinson's disease* often have oropharyngeal dysphagia, gastroesophageal reflux disease, esophageal dysphagia, constipation, and fecal incontinence. *Amyotrophic lateral sclerosis* and *myasthenia gravis* both can cause oropharyngeal dysphagia. More diffuse gastrointestinal tract dysmotility syndromes occur with poliomyelitis, Huntington's 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 French-Canadian ancestry) and *Duchenne's muscular dystrophy* can be complicated by oropharyngeal dysphagia. Duchenne's muscular dystrophy is associated with more widespread gastrointestinal tract dysmotility.

Rheumatologic

Involvement of the gastrointestinal tract in *scleroderma*, a common effect, is due to smooth muscle atrophy, fibrosis, small vessel vasculitis, and neural damage. Typically, the esophagus is affected (decreased motility, weak lower esophageal sphincter, gastroesophageal reflux disease, Barrett's esophagus, adenocarcinoma, and pill esophagitis). However, the stomach (gastroparesis), small bowel (bacterial overgrowth and pseudo-obstruction), and colon and rectum (decreased motility, megacolon, fecal incontinence and impaction, rectal prolapse, and anorectal sphincter dysfunction) also may be affected. Pancreatic exocrine secretion may decrease. Telangiectasias and diverticula may be found throughout the gastrointestinal tract, including gastric antral vascular ectasia, which is associated with connective tissue disease in general. Mild increases in aminotransferase levels, autoimmune liver disease, and primary biliary cirrhosis may be associated with scleroderma, as in other connective tissue diseases.

Gastrointestinal tract manifestations may occur in other connective tissue disorders such as *rheumatoid arthritis* (esophageal dysmotility; vasculitis with ischemic cholecystitis, appendicitis,

and colitis; and amyloidosis), *systemic lupus erythematosus* (esophageal dysmotility, gastrointestinal vasculitis, serositis, and pancreatitis), *polymyositis* (oropharyngeal dysmotility, gut smooth muscle dysfunction, and vasculitis), dermatomyositis (malignancies, including stomach, pancreas, ovary, lung, and colorectal), and *Sjögren's syndrome* (esophageal webs and pancreatic insufficiency). Rheumatoid arthritis may be part of *Felty's syndrome* (splenomegaly and neutropenia) with nodular regenerative hyperplasia and portal hypertension (variceal hemorrhage). *Nodular regenerative hyperplasia* itself also occurs with scleroderma, polymyalgia rheumatica, vasculitis, and lymphoproliferative or myeloproliferative syndromes. Rheumatoid arthritis also is associated with liver disease, including mild liver function test abnormalities, autoimmune chronic hepatitis, primary biliary cirrhosis, and amyloidosis (see below). Sjögren's syndrome is associated with autoimmune chronic hepatitis and primary biliary cirrhosis.

Patients with *seronegative spondyloarthropathies* may have ileocolonic inflammation similar to that of Crohn's disease. *Systemic vasculitides*, including *Behçet's syndrome* (oral and genital ulcers, gastrointestinal involvement similar to that of Crohn's disease, and Budd-Chiari syndrome), *polyarteritis nodosa* (gallbladder, pancreas, appendix, and ischemia involving the gastrointestinal tract; 50% of patients have hepatitis B virus infection), *Wegener's granulomatosis* (gastrointestinal tract), and *Churg-Strauss syndrome* (gallbladder and gastrointestinal tract), can have diverse gastrointestinal and hepatic manifestations.

Pregnancy and Gynecologic Conditions

Pregnancy has many effects on the gastrointestinal tract. Nausea and vomiting are extremely common during the first trimester of pregnancy. When these effects become protracted and severe (*hyperemesis gravidarum*), dehydration, weight loss, malnutrition, and liver function test abnormalities may occur (see Chapter 33, Liver Disease and Pregnancy). Risk factors include young age, obesity, multiparity, multiple births, first and molar pregnancies, and previous hyperemesis gravidarum. Hyperthyroidism must be excluded. Treatment is supportive, and symptoms usually resolve by week 20 of pregnancy.

Gastroesophageal reflux disease also is common during pregnancy because of the combined relaxing effects of estrogens and progestins on the smooth muscle of the body of the esophagus and the lower esophageal sphincter. Once symptoms occur during a pregnancy, they often persist until term and recur with subsequent pregnancies. Antacids (with avoidance of magnesium-containing antacids near term) and sucralfate appear safe, and, often, histamine$_2$-receptor blockers are used. Proton pump inhibitors probably are best avoided during pregnancy. Endoscopy rarely is indicated during pregnancy; if used, it is usually for substantial bleeding, intractable emesis, or persistent, severe upper abdominal pain. Lidocaine spray and meperidine (50 mg) are preferred as medications, although many use midazolam or diazepam. Fetal monitoring should be performed during endoscopic procedures, certainly after week 23. Pregnancy appears to decrease the frequency, severity, and risk of complications of *peptic ulcer disease*.

Constipation is another common gastrointestinal tract manifestation in pregnancy. Altered motility (hormonal), altered diet, constipating medications (iron), compression of the sigmoid colon by an enlarged uterus, and decreased activity all contribute. Treatment should include dietary advice, liquids, activity, fiber, and, if necessary, docusate- and magnesium-containing cathartics (except close to term). Castor oil (premature labor), mineral oil (maternal malabsorption of fat-soluble vitamins and severe aspiration pneumonia), and anthraquinones (possible malformations) should be avoided. Pregnancy is unlikely to cause *diarrhea*. Fiber, pectin, kaolin, and loperamide can be used, but diphenoxylate with atropine (Lomotil) and any bismuth-containing compound (Pepto-Bismol) should not be used. Colonoscopy should be avoided during pregnancy. Flexible sigmoidoscopy is thought by many to be safe. *Small-bowel obstruction* during pregnancy (about 1:1,500) is due most often to adhesions; *volvulus* is the second most common cause, especially in the third trimester, when incarcerated hernias are less common. *Appendicitis* is not more common during pregnancy (about 1:1,500), but the diagnosis often is delayed, with increased maternal (up to 11%) and fetal (up to 37%) mortality, especially late in pregnancy, when the enlarged uterus pushes the appendix and cecum up into the right upper quadrant, resulting in atypical signs and symptoms.

Endometriosis, if severe, often affects the gut; most frequently, the sigmoid colon is involved. It sometimes results in obstruction (adhesions), perforation, bleeding, diarrhea, and, more often, abdominal pain or constipation. These gastrointestinal 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. *Meigs' syndrome* presents with ascites and, often, pleural effusion in association with benign ovarian neoplasms.

Miscellaneous

Systemic amyloidosis includes AL amyloidosis (primary, myeloma, and plasma cell-related), AA amyloidosis (secondary, chronic infections, and inflammation), familial forms, dialysis-associated amyloidosis, and senile amyloidosis. Systemic forms can infiltrate the gastrointestinal tract, resulting in macroglossia (usually primary AL amyloidosis), esophageal dysphagia or dysmotility, gastroesophageal reflux disease, gastroparesis, gastric ulceration, tumors, bleeding, or obstruction, small- and large-bowel dysmotility or pseudo-obstruction, diarrhea, malabsorption, bacterial overgrowth, bleeding, ischemia, ulceration, constipation, and fecal incontinence. Liver involvement also is frequent, with hepatomegaly, increased alkaline phosphatase level, and, rarely, severe intrahepatic cholestasis (usually primary AL amyloidosis) or liver failure. Pancreatic exocrine insufficiency also has been described. Rectal, stomach, and liver (rare reports of rupture) biopsy findings often are diagnostic. Chemotherapy may be useful in treating primary AL amyloidosis, and colchicine may be useful in AA amyloidosis due to familial Mediterranean fever (fever, serositis, arthritis, vasculitis, and chest or abdominal pain; family history, recessive, chromosome band 16p13.3) and inflammatory bowel disease. Liver transplantation may be helpful for certain familial forms (ATTR or type I familial amyloid neuropathy, autosomal dominant, mutant transthyretin protein) with symptoms, but not after severe irreversible (especially neurologic) damage has occurred.

Ehlers-Danlos syndrome type IV, usually autosomal dominant, is associated often with bowel perforation, vascular aneurysms, arteriovenous fistulas, and rupture. *Paraneoplastic syndromes* with diffuse gastrointestinal 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. Antineuronal nuclear antibodies, type 1, usually are detectable.

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Miscellaneous Disorders

Questions and Answers

QUESTIONS

Abbreviations used:
CT, computed tomography
EGD, esophagogastroduodenoscopy
ESR, erythrocyte sedimentation rate
GERD, gastroesophageal reflux disease
HIV, human immunodeficiency virus
INR, international normalized ratio
MCV, mean corpuscular volume
MRA, magnetic resonance angiography
PPI, proton pump inhibitor
T_3/T_4, triiodothyronine/thyroxine

Multiple Choice (choose the best answer)

1. A 52-year-old man presents with hematemesis times 3. This occurred 24 hours after percutaneous transluminal coronary angioplasty and stenting for unstable angina. Currently, he takes aspirin, clopidogrel (Plavix), atenolol (Tenormin), and eptifibatide (IIB/IIIA receptor inhibitor). Blood pressure is 90/60 mm Hg, and the pulse rate is 120. The abdominal examination is otherwise unremarkable. Hemoglobin is 8.3 g/dL, platelet count 210,000/mm^3 (210×10^9/L), INR 1.1, and partial thromboplastin time 32 seconds. Your next step would be:

a. Upper endoscopy after blood transfusion
b. Fresh frozen plasma
c. Vitamin K intravenously
d. Platelet transfusions
e. Intravenous infusion of octreotide

2. A 60-year-old woman presents with melena times 4 over the past 12 hours. She takes 81 mg of aspirin daily for cerebrovascular disease. She has no history of gastrointestinal tract bleeding. She has no abdominal pain. On physical examination, supine blood pressure is 110/70 mm Hg, with a pulse rate of 105. Upon standing, blood pressure decreases to 90/60 mm Hg, with a pulse rate of 130. Abdominal examination findings are unremarkable. Rectal examination shows mushy black stool. Hemoglobin is 10.6 g/dL, MCV 89 fL, blood urea nitrogen 32 mg/dL, and creatinine 0.8 mg/dL. After 2 L of normal saline, the blood pressure is 120/85 mm Hg, with a pulse rate of 90. Upper endoscopy was performed. For which of the following findings would endoscopic injection of epinephrine and thermal therapy be appropriate?

a. An adherent clot in the anterior duodenal bulb
b. A 1-cm ulcer in the gastric antrum, with a flat red spot

c. A 1-cm ulcer high in the lesser curvature of the stomach, with a 3-mm nonbleeding visible vessel
d. A 1-cm ulcer in the gastric antrum, with a clean base
e. A 2-cm ulcer in the gastric antrum, with a flat black spot

3. Which patient(s) should receive prophylaxis for stress ulcer?

a. Patient with sepsis and acute renal failure
b. Patient with chronic renal failure and coronary artery disease who is receiving aspirin therapy
c. Patient on day #3 of mechanical ventilation for pneumonia
d. Patient on day #1 after cholecystectomy
e. Patient on day #2 after appendectomy who is receiving low-dose heparin therapy

4. A 34-year-old man presents with bleeding of a duodenal ulcer. He has a clean ulcer base, and a biopsy study confirms *Helicobacter pylori* infection. He receives 4 weeks of treatment with a PPI and 10 days of treatment with clarithromycin, PPI, and amoxicillin, all twice daily. To prove eradication of the *H. pylori* infection, which of the following should be done?

a. Repeat upper endoscopy and obtain biopsy specimens for histologic study 2 weeks after stopping PPI therapy
b. Urease breath test 1 week after stopping PPI therapy
c. *H. pylori* stool antigen at least 2 weeks after stopping PPI therapy
d. *H. pylori* serologic testing 1 week after stopping PPI therapy
e. *H. pylori* serologic testing 2 weeks after stopping PPI therapy

5. A 54-year-old man with no previous history of anemia presents with fatigue. Hemoglobin is 8.2 g/dL, MCV 71 fL, and serum ferritin 3 μg/L. Findings on upper endoscopy and colonoscopy into the terminal ileum are normal. Further testing should include which of the following?

a. Stool testing for occult blood
b. Computed tomography of the abdomen and pelvis
c. Capsule endoscopy
d. Small-bowel follow-through study
e. Barium enema

6. A 22-year-old woman previously in good health is evaluated for new-onset unilateral, throbbing, temporal headaches that are preceded by sensitivity to light and sound and nausea. The findings on physical examination, including a complete neurologic examination, are normal. The patient's mother has had similar headaches. The patient is given advice about medication. Several weeks later, she develops acute left lower quadrant pain, then several small-volume loose stools, first without blood then with "several tablespoons" of bright red blood. Most likely, which of the following was the advice she was given for her headaches?

a. At the first sign of an impending headache, take ibuprofen, 800 mg, by mouth
b. At the first sign of an impending headache, take sumatriptan, 100 mg, by mouth
c. Stop taking birth-control pills
d. Begin taking propranolol (Inderal), 20 mg, twice daily by mouth
e. Begin taking topiramate, 25 mg, by mouth, and increase by 1 tablet a week up to a maximum of 4 tablets twice daily

7. A 62-year-old previously healthy farmer develops acute bandlike constant pain across the top of his abdomen, with nausea and vomiting. He has been hospitalized for 3 weeks with necrotizing pancreatitis and is recovering. Early in the hospitalization, his gallbladder was removed for cholelithiasis. Now, dull, achy, persistent periumbilical pain; loose stools; nausea; and a poor appetite develop, just after he has resumed a full diet. He is afebrile. Physical examination findings are remarkable only for mild abdominal distention without tenderness to palpation. The serum levels of lipase and amylase are normal, as is the leukocyte count. Which of

the following is most likely to be found on abdominal/pelvic CT?

a. Thrombosis of the splenic vein
b. Organized pancreatic necrosis with air bubbles
c. Partial small-bowel obstruction
d. Thrombosis of the splenic vein and superior mesenteric vein
e. Peripancreatic 4-cm diameter oval fluid collection

8. A 50-year-old man with a history of lone atrial fibrillation undergoes screening colonoscopy. He has no history of hypertension, kidney disease, thyroid disease, coronary artery disease, or valvular heart disease. He takes no medications. He is prepared for the procedure with a phosphosoda-based preparation. The procedure shows a sessile, 3-mm polyp in the descending colon, which is removed by cold biopsy. Three hours after the procedure, a constant periumbilical pain develops. On examination, he appears uncomfortable, with blood pressure of 100/70 mm Hg, a pulse rate of 120 to 130, and an irregular rhythm. His abdomen has increased bowel sounds and is nontender to palpation. Which of the following is most likely?

a. Small-bowel ischemia due to an embolus
b. Small-bowel ischemia due to superior mesenteric venous thrombosis
c. Hypokalemia and hyperphosphatemia with cardiac dysfunction and low-flow ischemia of the small bowel
d. Perforation of the bowel
e. Gaseous distention of the bowel

9. A 62-year-old woman is evaluated for weight loss, diarrhea, and difficulty eating. Over the past year, she has lost 25 lb and feels "sick" when she eats, with nausea and vague, diffuse abdominal pain occurring 30 minutes after eating. She has been eating less and less. She reports watery, "slimy" stools. She has a history of severe coronary artery disease, hypertension, peripheral vascular disease, cigarette smoking, moderate alcohol use, and mild renal insufficiency. Results of endoscopy with small-bowel biopsy and colonoscopy with terminal ileal views are unremarkable. MRA shows high-grade lesions of the proximal celiac artery and superior mesenteric artery. The pancreas and liver are normal. The serum level of creatine is 1.7 mg/dL. Which of the following would most likely benefit this patient?

a. A 72-hour fecal fat study
b. Oral pancreatic enzyme therapy
c. An abdominal-pelvic CT scan without intravenous contrast but with oral contrast
d. An abdominal-pelvic CT scan with oral and IV contrast after intravenous hydration and acetylcysteine therapy
e. Mesenteric angiography after intravenous hydration and acetylcysteine therapy

10. A 26-year-old man from Japan has recurrent abdominal pain, diarrhea, oral ulcers, firm tender reddish nodules on his shins, and now photophobia with conjunctival erythema surrounding the limbus of both eyes. The day after phlebotomy, a pustule is noted at the venipuncture site. Which of the following is most likely?

a. At colonoscopy, focal ulcerations are found in the ileocecal region, and biopsy findings are consistent with chronic active colitis, with granulomas
b. Findings on complete ophthalmologic examination are normal
c. Scrotal examination shows an ulcer
d. The oral ulcers are due to herpes simplex infection
e. He has several relatives with Crohn's disease

11. A 69-year-old woman presents with a 3-day history of abdominal pain, retching, and inability to eat. A prominent gastric air bubble is seen on an abdominal radiograph. A nasogastric tube could not be passed. She has a history of hiatal hernia and GERD. Physical examination findings are noncontributory, and laboratory results are remarkable for a white blood cell count of 15,000/mm^3 (15×10^9/L).

The most likely diagnosis is:

a. Gastric volvulus
b. Gastric outlet obstruction
c. Duodenal ulcer
d. Refractory GERD
e. Celiac disease

12. A 55-year-old man presents with a 6-month history of nausea, vomiting, diarrhea, and abdominal pain. The symptoms are worse with ingestion of alcohol. He also reports a pruritic rash. Scattered cutaneous brown-red macules are found on physical examination. At endoscopy, multiple postbulbar duodenal ulcers are found. Which test is most likely to provide the correct diagnosis?

a. 24-Hour urine for 5-hydroxyindoleacetic acid
b. Serum gastrin
c. Serum calcitonin
d. Octreotide scan
e. Serum tryptase level

13. A 52-year-old man from Nigeria has a 6-month history of fever, a 20-lb weight loss, and malaise. On physical examination, his abdomen is diffusely tender and doughy. Hemoglobin is 10.2 g/dL, ESR 45 mm/hour, and albumin 2.1 g/dL. Abdominal CT shows ascites and thickened loops of distal small bowel. Paracentesis of the ascites discloses a protein level of 3.0 g/100 mL, albumin 1.9 g/100 mL, glucose 30 mg/dL, and a cell count of 350 cells/mm^3 (0.35×10^9/L), with 60% lymphocytes. The most appropriate next step is:

a. High-dose corticosteroids
b. Intravenous antibiotics
c. EGD with biopsy
d. Laparoscopy
e. Liver biopsy

14. A 42-year-old woman with HIV infection, recently diagnosed after she presented with *Candida* esophagitis, now has diarrhea with blood streaks, abdominal pain, fever, and malaise. Which of the following will most likely lead to the correct diagnosis?

a. Stool examination for *Cryptosporidium*
b. EGD for Kaposi's sarcoma
c. Blood culture for *Mycobacterium avium-intracellulare*
d. Colonoscopy for cytomegalovirus
e. Stool examination for *Candida*

15. A 53-year-old woman presents for evaluation of recent-onset constipation. She also reports postprandial fullness. Colonoscopy findings from 1 year ago were negative. She states that she has had an involuntary weight loss of 20 lb. She has smoked for years. Finger clubbing is noted on physical examination. Hemoglobin is 12.0 g/dL, ESR 85 mm/hour; and thyroid-stimulating hormone and calcium levels are normal. What test is most likely to lead to a diagnosis?

a. Serum angiotensin-converting enzyme level
b. Parathyroid hormone level
c. Free T_3/T_4 levels
d. Anti-neuronal nuclear antibody
e. Repeat colonoscopy

16. A 46-year-old man is evaluated after four self-limited episodes of acute, poorly localized abdominal pain accompanied by nausea and diarrhea. He has no history of fever, weight loss, or previous surgery but does have a history of early uncomplicated chronic lymphocytic leukemia. Abdominal CT during his fourth episode showed some edema of the small bowel without obstruction and mild ascites. Results of follow-up abdominal ultrasonography 2 days later are normal, with no ascites. Which of the following tests is most likely to be helpful during an episode of abdominal pain?

a. Syphilis serology
b. Serum lead level
c. Serum aminolevulinic acid level
d. Serum C4 level
e. Urgent paracentesis

17. A 22-year-old gravida 1 para 0 woman at week 29 of pregnancy reports increasing constipation. Before her pregnancy, she would suffer from constipation once or twice a month and obtain relief with a laxative. Her mother died of colon cancer at age 55 years. The patient states that she has not had any previous difficulty expelling stool or manual disimpaction. The complete blood count and thyroid-stimulating hormone and calcium levels are normal. She has not had a bowel movement for 2 days and feels bloated. Physical examination findings are unremarkable. Which of the following would be best to do next?

a. Colonoscopy
b. Flexible sigmoidoscopy
c. Mineral oil
d. Senna or cascara
e. Milk of magnesia

ANSWERS

1. Answer d
IIB/IIIA Receptor inhibitors block the final pathway of platelet aggregation, leading to essentially complete inhibition of platelet function. These effects are reversed with the transfusion of platelets. The platelet effect of eptifibatide generally resolves in 12 hours. The most appropriate management would be infusion of platelets. If bleeding continues after that point, proceed with endoscopy.

2. Answer a
Endoscopic treatment is appropriate for active bleeding, nonbleeding visible vessels, and in management of an adherent clot. The adherent clot in the anterior bulb would be amenable to endoscopic therapy. A nonbleeding visible vessel of 3 mm on the lesser curvature of the stomach likely is associated with the left gastric artery and is too large to be coagulated reliably.

3. Answer c
High-risk medical groups for prophylaxis for stress ulcer are patients with respiratory failure that requires ventilation for more than 48 hours and coagulopathy (INR >1.5, platelet count <50,000/mm^3 [50×10^9/L] before the administration of anticoagulation medication).

4. Answer c
Repeat histologic study is quite accurate, but endoscopy is costly and would not be indicated for follow-up of a duodenal ulcer. Both the urease breath test and *H. pylori* stool antigen are cost-effective techniques for proving the eradication of *H. pylori* infection. These should be performed at least 2 weeks after PPI therapy has been stopped because this therapy can suppress *H. pylori* infection. Results of serologic testing generally remain positive despite eradication, and this is not a good test to confirm the resolution of an *H. pylori* infection.

5. Answer c
New iron deficiency in a male requires further evaluation. Small-bowel follow-through has a yield of less than 10%. Computed tomography of the abdomen and a barium enema would be of minimal benefit. Further evaluation would be indicated even if heme were negative. Capsule endoscopy is the test with the highest yield in the evaluation of iron deficiency anemia and would be the test of choice in this setting. Celiac disease should be excluded as well.

6. Answer b
This clinical scenario is most consistent with migraine headaches with subsequent ischemic colitis. As a nonsteroidal antiinflammatory drug, ibuprofen can cause mucosal damage throughout the gastrointestinal tract, but this would be an unusual presentation. Propranolol (Inderal) and topiramate are not associated with ischemic colitis, but triptans such as sumatriptan are. If this young woman stopped taking birth-control pills, it would not predispose her to ischemic colitis. However starting treatment with hormonal medications, particularly in women with a personal or family history of a hypercoagulable state, could result in ischemic colitis.

7. Answer d
This patient most likely had acute gallstone pancreatitis with pancreatic necrosis, but he has nearly recovered and is beginning to take a full diet. It is unlikely that the necrotic pancreatic tissue is infected, because he does not have a fever or an

increased leukocyte count. Thrombosis of the splenic vein alone would not cause these symptoms, nor would a small peripancreatic fluid collection. The lack of vomiting or colicky pain and the occurrence of diarrhea are unlikely to be due to small-bowel obstruction. With necrotizing pancreatitis, he is at risk for splenic vein and superior mesenteric vein thrombosis, the latter resulting in small-bowel congestion, with dull, poorly localized, persistent achy discomfort; nausea; poor appetite; and loose stools.

8. Answer a

Although this patient is at low risk for embolization, the clinical presentation with acute, poorly localized mid-gut pain without tenderness and an irregular pulse suggests acute mesenteric ischemia of the small bowel. The 3-hour interval since colonoscopy makes gaseous distention unlikely. Also, perforation from cold biopsy of a diminutive polyp is unlikely. He has no history to suggest venous thrombosis of the superior mesenteric vein; also, it is unlikely that electrolyte abnormalities from the phosphosoda preparation would cause cardiac dysfunction and a low-flow state in this otherwise healthy 50-year-old man.

9. Answer e

This patient most likely has chronic mesenteric ischemia with postprandial pain due to limited arterial blood flow to the small bowel, especially when increased blood flow is needed after meals. CT will not add anything to MRA. A fecal fat study may be abnormal, but it will not help treat the situation. The patient is unlikely to have pancreatic insufficiency despite her history of alcohol use. The recurrent postprandial pain has a mid-gut distribution most consistent with abdominal angina. At angiography, a decision can be made in this high-risk surgical patient to pursue angioplasty with or without stenting or surgery to bypass the proximal arterial large-vessel occlusive lesions.

10. Answer c

This patient most likely has Behçet's syndrome with vasculitic involvement of the gastrointestinal tract. As in Crohn's disease, focal ulceration of the ileocecal region can occur, with pain and diarrhea, but granulomas are not typically seen in biopsy specimens. With all these symptoms, the eye examination findings should not be normal but show uveitis, which tends to be a panuveitis in Behçet's syndrome in contrast to the anterior uveitis of Crohn's disease. Oral ulcers in Behçet's syndrome are not due to herpes simplex infection. The patient would be unlikely to have several relatives with Crohn's disease. Genital ulcers, including scrotal ulcers in men, are seen much more often in Behçet's syndrome than in Crohn's disease. Erythema nodosum is seen in both Crohn's disease and Behçet's syndrome, and in Behçet's syndrome, they may be a clue to the presence of visceral vasculitis.

11. Answer a

This patient has Borchardt's triad, which consists of abdominal pain, retching without vomitus, and inability to pass a nasogastric tube. The other disorders could cause pain and retching, but not the inability to pass a nasogastric tube. The history is quite acute for refractory GERD or celiac disease. Vomiting would occur often with gastric outlet obstruction. Surgical consultation would be indicated for acute gastric volvulus.

12. Answer e

An increased serum level of gastrin could be suggestive of Zollinger-Ellison syndrome; an increased urine concentration of 5-hydroxyindoleacetic acid, of carcinoid syndrome; and an increased serum level of calcitonin, of medullary thyroid cancer. All these could include diarrhea, but the rash (urticaria pigmentosa) is typical of systemic mastocytosis, with diarrhea, hypersecretion of gastric acid (ulcers), and an increased serum level of tryptase. An octreotide scan would not be useful.

13. Answer d

The ascitic fluid analysis suggests a peritoneal process. Because of the 6-month history, tuberculosis or malignancy are likely, and laparoscopy affords the best chance for a diagnosis, compared with endoscopy or liver biopsy (low yield). Corticosteroid or antibiotic therapy has no role (most of the cells are lymphocytes).

14. Answer d

Cryptosporidiosis does not cause bloody diarrhea. Kaposi's sarcoma of the gastrointestinal tract can

bleed, but does not cause diarrhea. Infection with *Myobacterium avium-intracellulare* complex usually occurs much later in very advanced immunosuppressed HIV patients. *Candida* can be found in normal stool and does not cause bloody diarrhea. The case presentation is most consistent with CMV infection.

15. Answer d

The new constipation, weight loss, clubbing, anemia, and increased ESR are suggestive of malignancy. A paraneoplastic syndrome with gastrointestinal dysmotility is likely, and the anti-neuronal nuclear antibody (ANNA-1) test is a noninvasive test that, in this patient, is likely to lead to a diagnosis, for example, of small cell lung cancer.

16. Answer d

Acute attacks of poorly localized abdominal pain in a person with no history of abdominal surgery could be due to syphilis, lead poisoning, or porphyria (aminolevulinic acid level). However, the transient small-bowel edema and ascites are suggestive of angioedema, which in this case may be acquired rather than congenital, secondary to the patient's lymphoproliferative disorder. During an attack, the levels of C4 and total complement should be decreased, and deficient C1 esterase inhibitor levels (quantitative or qualitative) could confirm the diagnosis.

17. Answer e

There is no reason to perform a procedure. The patient most likely has late pregnancy-associated constipation. Mineral oil should be avoided in pregnancy (aspiration, fat-soluble vitamin malabsorption), as should anthraquinone laxatives (malformation). Milk of magnesia is safe until the onset of labor and delivery.

Section V

Colon

CHAPTER 14

Inflammatory Bowel Disease: Clinical Aspects

William J. Tremaine, MD

Ulcerative colitis is an idiopathic chronic inflammatory disorder of the colonic mucosa, with the potential for extraintestinal inflammation. The disease extends proximally from the anal verge in an uninterrupted pattern to involve all or part of the colon.

Crohn's disease is an idiopathic chronic inflammatory disorder of the full thickness of the intestine, most commonly in the ileum and the colon, with the potential to involve the gastrointestinal tract at any level from the mouth to the anus and perianal region. There is also the potential for extraintestinal inflammation. Typically, there is patchy disease in the gastrointestinal tract, with intervening areas of normal mucosa.

EPIDEMIOLOGY

Men and women are generally at similar risk for inflammatory bowel disease (IBD). Onset of IBD is highest among adolescents; the peak incidence is between ages 15 and 25 years. IBD is more common among Ashkenazi Jews than non-Jews. The incidence and prevalence of ulcerative colitis are similar in a given location, but the values vary depending on the patient population of the reporting center. The prevalence of the disease is much higher than the incidence for several reasons: disease onset is often in young adults and children, the disease is chronic and lifelong, and the mortality rate associated with the disease is low. In Europe and North America, the incidence of ulcerative colitis and Crohn's disease roughly doubled during the 1960s and 1970s, and the incidence for both conditions has been relatively stable since that time. With this doubling of the incidence, the prevalence also increased, and it will be several more decades before the prevalence levels off.

The incidence of ulcerative colitis is 7.3 per 100,000 in Olmsted County, Minnesota, and 14.0 per 100,000 in Winnipeg, Manitoba. The prevalence in Olmsted County, Minnesota, is 181 per 100,000. The proportion of patients with ulcerative proctitis varies in different series from 17% to 49% of the totals.

The incidence of Crohn's disease also varies among different reporting centers. It is 5.8 per 100,000 in Olmsted County and 15.0 per 100,000 in Winnipeg, and the prevalence in Olmsted County is 133 per 100,000.

Abbreviation: IBD, inflammatory bowel disease.

Mortality rates with IBD are slightly higher than those for the general population. In a study from Stockholm, the standardized mortality ratio was 1.37 for ulcerative colitis and 1.51 for Crohn's disease.

GENETICS

From 10% to 15% of patients with ulcerative colitis have a relative with IBD, mainly ulcerative colitis and, less commonly, Crohn's disease. About 15% of patients with Crohn's disease have a relative with IBD, mainly Crohn's disease and, less commonly, ulcerative colitis. 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 Crohn's disease and in less than 15% of controls. 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. Other genetic linkages have been identified, but so far the phenotypes have not been characterized. Three genetic syndromes are associated with IBD: Turner's syndrome, Hermansky-Pudlak syndrome (oculocutaneous albinism, a platelet aggregation defect, and a ceroidlike pigment deposition), and glycogen storage disease type 1B.

DIET

Patients have no specific dietary restrictions. Although lactose intolerance is more common with Crohn's disease than in 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. Corticosteroids are superior to enteral nutrition for the treatment of Crohn's disease. Parenteral nutrition has not been found to be superior to enteral nutrition for Crohn's disease. The role of enteral and parenteral nutrition as primary therapy for Crohn's disease is controversial, and they are used primarily as an alternative to corticosteroids. There is no convincing evidence that elemental or parenteral nutrition is therapeutic for ulcerative colitis.

PREGNANCY

Fertility is normal in inactive ulcerative colitis and Crohn's disease. 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: although most studies do not show an increased risk in association with the disease or the treatments, one study found more birth defects among the offspring of fathers with Crohn's disease who took 6-mercaptopurine. The course of pregnancy is usually normal, although there is an increased chance of a preterm delivery and decreased birth weight. For women with IBD in remission before pregnancy, two-thirds remain in remission through the pregnancy and postpartum. Flares occur most commonly during the first trimester and postpartum. 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.

ENVIRONMENTAL INFLUENCES

Ulcerative colitis is primarily a disease of nonsmokers. Only 13% of patients with ulcerative colitis are current smokers, and the rest are nonsmokers or former smokers. Pouchitis after proctocolectomy with an ileal J pouch-to-anal anastomosis for ulcerative colitis is less common among smokers. In contrast, patients with Crohn's disease 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, and pathology

studies, and the specific diagnostic tests are based on the presenting symptoms and physical examination findings.

CLINICAL PRESENTATIONS

Ulcerative Colitis

The onset 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 a day, 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's Disease

Symptoms 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 Crohn's disease 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 Crohn's disease include dysphagia, odynophagia, and chest pain, even without eating. The findings of perianal Crohn's disease include perirectal abscess, painful and edematous external hemorrhoids, and anal and perianal fistulas. Enterovesical fistulas can cause pneumaturia and recurrent urinary tract infections. Rectovaginal fistulas occur in up to 10% of women with rectal Crohn's disease and may cause gas or stool to be passed from the vagina. In children, the onset of Crohn's disease is often insidious; weight loss occurs in up to 87% before the diagnosis, and 30% of children have growth failure before the onset of intestinal symptoms.

Physical Examination

In mildly active ulcerative colitis, 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, dehydration, tachycardia, fever, diminished bowel sounds, and diffuse abdominal tenderness with rebound. Tenderness with rebound is ominous and suggests toxic dilatation or perforation. In Crohn's disease, physical examination findings may be normal or include one 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, violaceous external hemorrhoidal tags; fistulas; anal canal fissures; and anal stenosis. Ulcers in Crohn's disease may occur on the lips, gingiva, or buccal mucosa. Physical examination findings due to the extraintestinal manifestations of IBD are discussed in Chapter 16 (Inflammatory Bowel Disease: Extraintestinal Manifestations and Cancer).

Laboratory Findings

In mild disease, laboratory results may be normal. Iron deficiency anemia due to gastrointestinal tract blood loss may occur in ulcerative colitis and Crohn's disease, 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 for anemia in patients with Crohn's disease. 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.

Acute phase reactants, including the erythrocyte sedimentation rate, C-reactive protein, and orosomucoid, usually correlate with disease activity but may be normal in mildly active disease. The perinuclear antineutrophil cytoplasmic antibody is positive in about two-thirds of patients with ulcerative colitis and about one-third of patients with Crohn's disease. The anti-*Saccharomyces cerevisiae* antibody is positive in about two-thirds of patients with Crohn's disease and about one-third of patients with ulcerative colitis. These tests may be used together to help distinguish ulcerative colitis from Crohn's disease. However, the positive predictive value of the two tests together is 63.6% for ulcerative colitis and 80% for Crohn's disease; thus, distinguishing the two diseases with these serologic tests is less than ideal (Table 1). 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.

Endoscopy

Flexible proctosigmoidoscopy or colonoscopy can identify characteristic mucosal changes of ulcerative colitis, including loss of the normal vascular markings, mucosal granularity, friability, mucous exudate, and focal ulceration (Fig. 1). With colonoscopy, the extent of disease can be determined and the terminal ileum can be examined for evidence of backwash ileitis in ulcerative colitis or ileal involvement in Crohn's disease. Patients with left-sided ulcerative colitis may have inflammatory changes around the appendix, called a *cecal patch*, as a manifestation of the disease; this finding should not be confused with segmental colitis due to Crohn's disease. Only a limited examination of the rectosigmoid colon should be performed in patients with severely active colitis, because of the risk of perforation or hemorrhage with an extensive examination. In Crohn's disease, 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 (Fig. 2). Upper gastrointestinal endoscopy can confirm the presence and distribution of disease in the upper gut and define how severely the mucosa is affected. Wireless capsule endoscopy is useful in making the diagnosis of small-bowel Crohn's disease in some patients, but its precise role in the work-up of IBD has not been defined.

In Crohn's disease, the endoscopic findings do not correlate closely with clinical disease activity. For patients with ulcerative colitis (extending proximal to the rectum), the risk of malignancy is increased above that for the general population after 8 to 10 years of disease. For that reason, periodic colonoscopy with biopsies for surveillance for dysplasia is indicated after 8 to 10 years of disease. The risk of malignancy for patients with less extensive ulcerative colitis (with involvement of the colon distal to the splenic flexure) also is increased, but the magnitude of the risk is not defined. There does not appear to be an increased risk of rectal cancer for ulcerative proctitis without colitis above the rectum. Patients with left-sided ulcerative colitis of 8 to 10 years' duration, or longer, should undergo periodic surveillance biopsies. The optimal interval between surveillance examinations has not been defined, and the examinations usually are performed at 1- to 2-year intervals.

Table 1. Positive Predictive Value of Serologic Markers in Patients With Indeterminate Colitis

Disease	Marker	Positive predictive value, %
Ulcerative colitis	pANCA+ ASCA–	63.6
Crohn's disease	pANCA– ASCA+	80

*ASCA, anti-*Saccharomyces cerevisiae *antibody; pANCA, perinuclear antineutrophil cytoplasmic antibody.*

Radiologic Features

Plain abdominal films with supine and upright views should be obtained in cases of severely active

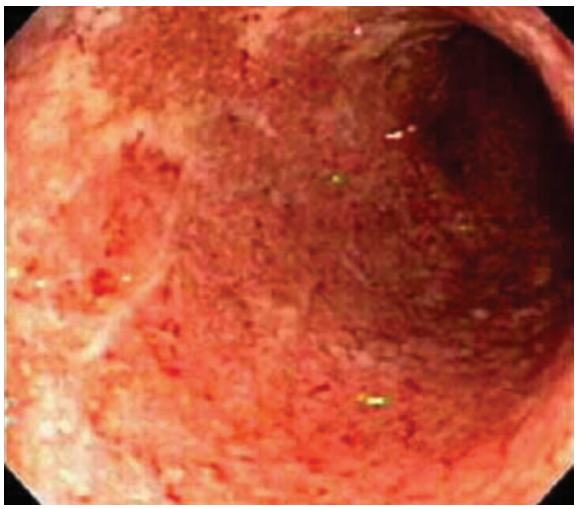

Fig. 1. Diffuse changes of colitis include mucosal granularity and erythema, with mucus exudate. This is typical of moderately active ulcerative colitis.

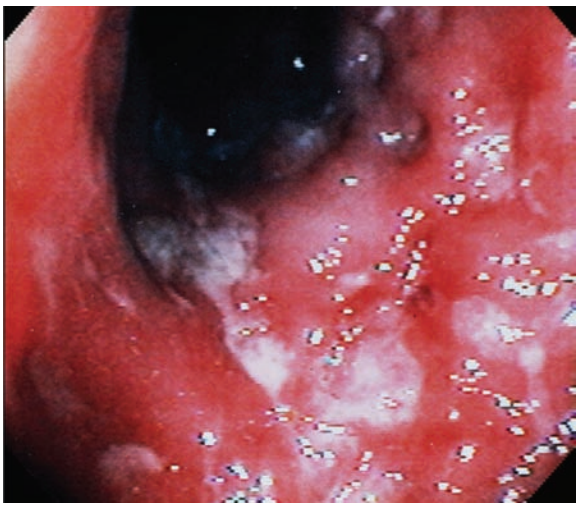

Fig. 2. Linear ulcers and surrounding mucosal erythema, edema, and granularity. This is typical of Crohn's disease.

colitis to examine for complications, including perforation with free air and toxic dilatation with a luminal diameter of 5 cm or more. In Crohn's disease, computed tomographic enterography (Fig. 3) can identify the location and extent of disease and complications such as fistulas, strictures, or abscesses. Alternative studies are small intestinal enteroclysis, a single-contrast small-bowel follow-through examination, and an air contrast barium enema. A barium swallow may be useful for assessment of Crohn's disease that involves the esophagus, stomach, and duodenum. Abdominal computed tomography and ultrasonography are useful for identifying intra-abdominal abscesses. Magnetic resonance imaging is superior to computed tomography for identifying pelvic and perianal abscesses as well as intra-abdominal Crohn's disease and abscesses.

Histology

Mucosal biopsy specimens from involved areas of the gastrointestinal tract are useful for excluding self-limited colitis and other infections and noninfectious colitis due to ischemia, collagenous and lymphocytic colitis, drug effect, radiation injury, and solitary rectal ulcer syndrome. Noncaseating granulomas are a feature of Crohn's disease and can be helpful for distinguishing it from ulcerative colitis, but even when multiple specimens are taken, granulomas are identified in only 30% of resected Crohn's disease specimens. The presence of focal, patchy inflammation with normal intervening mucosa is characteristic of Crohn's disease but not invariably identifiable.

Differential Diagnosis

Ulcerative colitis and Crohn's disease must be distinguished from infectious causes of colitis and also from the noninfectious causes of inflammation in

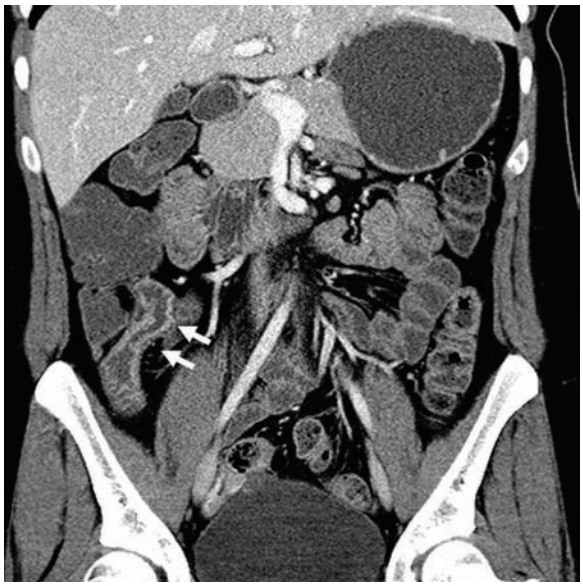

Fig. 3. Coronal computed tomographic enterography showing distal ileal hyperenhancement and wall thickening (*arrows*) of active inflammatory Crohn's disease.

the colon and small intestine (Table 2). *Microscopic colitis* is a descriptive term for 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 there are intraepithelial lymphocytes and chronic inflammatory cells 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 Crohn's disease. Ischemia more commonly causes segmental colitis that may be confused with Crohn's disease, but occasionally it can cause a diffuse colitis that can appear as ulcerative colitis. Injury to the rectum from radiation for prostate cancer or gynecologic malignancy may appear as ulcerative proctitis or Crohn's disease with fistulas and strictures. Injury to the small intestine and more proximal colon from radiation may cause chronic diarrhea, strictures, malabsorption, and other features that may mimic extensive Crohn's disease. Solitary rectal ulcer syndrome may be confused with Crohn's disease involving the rectum but can be differentiated on the basis of histologic features showing marked subepithelial fibrosis without inflammation. Diverticulitis may mimic Crohn's disease with fistulas, localized abscesses, and segmental colitis. In addition, patients with diverticulitis may have extraintestinal symptoms, just as patients with IBD.

Table 2. Differential Diagnosis of Inflammatory Bowel Disease

Acute self-limited colitis
Bacteria
Toxigenic *Escherichia coli*
Salmonella
Shigella
Campylobacter
Yersinia
Mycobacterium
Neisseria gonorrhoeae
Clostridium difficile
Parasites
Amebiasis
Chlamydia
Viruses
Cytomegalovirus
Herpes simplex
Collagenous/lymphocytic colitis
Diverticular disease-associated colitis
Medication-induced
Nonsteroidal antiinflammatory drugs
Gold
Ischemic colitis
Radiation enterocolitis
Diverticulitis
Appendicitis
Neutropenic enterocolitis
Solitary rectal ulcer syndrome
Malignancy
Carcinoma
Lymphoma
Leukemia

RECOMMENDED READING

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CHAPTER 15

Inflammatory Bowel Disease: Therapy

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Many different medical and surgical therapies are available for inflammatory bowel disease. Medical therapies include antiinflammatory drugs such as sulfasalazine, olsalazine, balsalazide, and mesalamine; antibiotics; corticosteroids, including budesonide; immunosuppressive medications such as azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, and tacrolimus; and biotechnology medications such as infliximab and adalimumab. Surgical therapies include colectomy with ileostomy, ileoanal pouch, or Kock pouch for ulcerative colitis and surgical resection, stricturoplasty, and placement of setons for Crohn's disease.

Many of the treatments for ulcerative colitis and Crohn's disease are designed to deliver medications topically to the inflamed bowel, with the goal of achieving local efficacy with minimal systemic absorption, thus minimizing toxicity. A thorough understanding of the anatomical classification of both ulcerative colitis and Crohn's disease is required in order to choose the optimal drug delivery system for a patient.

Ulcerative colitis can be divided into *ulcerative proctitis* (rectal involvement only, with the maximal extent of 10 cm from the anal verge), *ulcerative proctosigmoiditis* (inflammation is limited to the rectum and sigmoid colon), *left-sided ulcerative colitis* (inflammation does not extend proximal to the splenic flexure), and *extensive colitis* or *pancolitis* (inflammation extends proximal to the splenic flexure or involves the entire colon). Crohn's disease can be divided into *Crohn's ileitis* (only the small bowel is involved), *Crohn's colitis* (only the colon is involved), and *Crohn's ileocolitis* (both the small bowel and colon are involved).

ANTIINFLAMMATORY MEDICATIONS (5-AMINOSALICYLATES)

Sulfasalazine, oral mesalamine (Pentasa, Asacol, and Lialda), rectal mesalamine (Rowasa and Canasa), olsalazine, and balsalazide are drugs that deliver 5-aminosalicylate (mesalamine) to the colon (Table 1). Sulfasalazine, the first drug developed in this class, was designed to combine the antiinflammatory properties of 5-aminosalicylate with the antibacterial properties of sulfapyridine for the treatment of rheumatoid arthritis. Subsequently, sulfasalazine was discovered to be effective for ulcerative colitis and to serve as a

Abbreviations: CIR, controlled ileal release; TNF, tumor necrosis factor.

Table 1. 5-Aminosalicylate (5-ASA) Preparations for Treating Ulcerative Colitis (UC)

Generic name	Proprietary name	Formulation	Sites of delivery	Daily dose, g*		Indication
				Active	Maintenance	
Mesalamine	Rowasa	Enema suspension	Distal to splenic flexure	4	1-4	Active distal UC Remission maintenance distal UC
	Canasa	Suppository	Rectum	1-1.5	0.5-1	Active proctitis Remission maintenance distal UC
	Asacol	Eudragit-S–coated tablets (release at pH ≥7.0)	Terminal ileum, colon	1.6-4.8	0.8-4.8	Active UC Remission maintenance UC
	Pentasa	Ethylcellulose-coated microgranules (time- and pH-dependent release)	Duodenum, jejenum, ileum, colon	2-4	1.5-4	Active UC Remission maintenance UC
	Lialda	Eudragit-S–coated tablets (release at pH ≥7.0) and lipophilic and hydrophilic matrices	Terminal ileum, colon	2.4-4.8	2.4	Active UC Remission maintenance UC
Olsalazine	Dipentum	5-ASA dimer linked by azo bond	Colon	2-3	1	Remission maintenance UC
Sulfasalazine	Azulfidine	5-ASA linked to sulfapyridine by azo bond	Colon	2-4	2-4	Active UC Remission maintenance UC
Balsalazide	Colazal	5-ASA linked to inert carrier by azo bond	Colon	2-6.75	2-6.75	Active UC Remission maintenance UC

**Dose ranges reflect those commonly used in clinical practice and are broader than those specifically studied in clinical trials.*

prodrug for the active ingredient 5-aminosalicylate. 5-Aminosalicylate is linked to sulfapyridine by an azo bond that is cleaved by bacteria in the colon. Olsalazine and balsalazide are also prodrugs for 5-aminosalicylate. Olsalazine consists of a dimer of two 5-aminosalicylate molecules linked by an azo bond. Balsalazide consists of 5-aminosalicylate linked to an inert carrier by an azo bond. Parent 5-aminosalicylate (mesalamine) can be delivered orally in a capsule covered with the pH-dependent polymer Eudragit-S, which dissolves at pH 7 in the terminal ileum and cecum (Asacol), as ethylcellulose-coated granules that give a timed release throughout the gastrointestinal tract, beginning in the duodenum, jejunum, and ileum and ending in the colon and rectum (Pentasa), or as a tablet covered with the pH-dependent polymer Eudragit-S, which dissolves at pH 7 in the terminal ileum and cecum, exposing lipophilic and hydrophilic matrices that reportedly prolong mesalamine release throughout the colon (Lialda). Mesalamine can be administered also as an enema (Rowasa) or a suppository (Canasa).

In placebo-controlled trials, sulfasalazine at doses of 2 to 6 g daily is effective in both inducing remission in mildly to moderately active ulcerative colitis and maintaining remission. In comparative trials, sulfasalazine is less effective than oral corticosteroids for active ulcerative colitis. In contrast, placebo-controlled trials of sulfasalazine at 3 to 5 g daily for mildly to moderately active Crohn's disease demonstrated only modest efficacy for inducing remission (this effect was limited to patients with Crohn's colitis or ileocolitis). In comparative trials, sulfasalazine was less effective than oral corticosteroids for active Crohn's disease. Sulfasalazine at 2.5 to 3 g daily was not more effective than placebo for maintaining remission in Crohn's disease. Drug-associated toxicity occurs in up to 30% of patients receiving treatment with sulfasalazine. Commonly observed adverse events include headache, epigastric pain, nausea and vomiting, and skin rash. Less common but severe adverse events include hepatitis, fever, autoimmune hemolysis, aplastic anemia, leukopenia, agranulocytosis, folate deficiency, pancreatitis, drug-induced lupus, pneumonitis, and Stevens-Johnson syndrome. Reversible male infertility may occur. Sulfasalazine may be taken during pregnancy and breastfeeding.

Similar to those for sulfasalazine, placebo-controlled trials of mesalamine enemas, 1 to 4 g daily, and mesalamine suppositories, 0.5 to 1.5 g daily, have demonstrated efficacy for both inducing remission in mildly to moderately active left-sided ulcerative colitis and ulcerative proctitis and maintaining remission. Oral mesalamine delivered to the terminal ileum and cecum (Asacol and Lialda) at doses of 1.6 to 4.8 g daily or throughout the gastrointestinal tract (Pentasa) at 2 to 4 g daily in patients with mildly to moderately active ulcerative colitis is effective for inducing remission, and Asacol, 0.8 to 1.6 g daily, and Pentasa, 4 g daily, are effective for maintaining remission.

The data for use of oral mesalamine in the treatment of Crohn's disease are less clear. Placebo-controlled trials have shown that low-dose mesalamine (1-2 g daily) is not effective for inducing remission in mildly to moderately active Crohn's disease. Data from placebo-controlled trials for high-dose mesalamine (3.2-4 g daily) for inducing remission in active Crohn's disease are conflicting (if there is benefit, it is relatively small). A comparative trial demonstrated that oral mesalamine is less effective than controlled ileal release (CIR) budesonide, 9 mg daily, for active Crohn's disease. Data from placebo-controlled trials of oral mesalamine, 1 to 4 g daily, for maintenance of medically induced remission or postoperative remission of Crohn's disease are conflicting (however, a meta-analysis has suggested a small benefit for postoperative maintenance of remission). Oral mesalamine, 4 g daily, is not steroid-sparing.

Placebo-controlled trials have shown that olsalazine at 0.75 to 3 g daily is effective for inducing remission in patients with mildly to moderately active ulcerative colitis. Placebo-controlled trials have demonstrated that olsalazine at 1 g daily is effective for maintaining remission in ulcerative colitis. Comparative trials have shown that balsalazide at 6.75 g (contains 2.4 g of 5-aminosalicylate) daily has an efficacy similar to that of oral mesalamine at 2.4 g daily for inducing remission in mildly to moderately active ulcerative colitis. Dose-response trials demonstrated that balsalazide at 4 to 6 g daily is more effective than balsalazide at 2 to 3 g daily for maintaining remission in ulcerative colitis (this evidence of dose response demonstrates

a maintenance benefit for balsalazide even though a placebo-controlled trial has not been performed).

Olsalazine, balsalazide, and mesalamine generally are better tolerated than sulfasalazine. Commonly occurring adverse events include headache and gastrointestinal symptoms attributable to underlying inflammatory bowel disease. Sometimes, rash, alopecia, and a hypersensitivity reaction resulting in a syndrome of worsening diarrhea and abdominal pain may occur. Rarely, serious adverse events, including interstitial nephritis, pericarditis, pneumonitis, hepatitis, and pancreatitis, are observed. Ileal secretory diarrhea can occur with olsalazine. Olsalazine, balsalazide, and mesalamine may be taken during pregnancy and breastfeeding.

ANTIBIOTICS

Controlled trials of various antibiotics, including vancomycin, metronidazole, ciprofloxacin, and tobramycin, have not demonstrated efficacy in ulcerative colitis. Thus, as a primary treatment for ulcerative colitis, antibiotic therapy is not appropriate. The data for use of antibiotics in Crohn's disease are less clear cut. Three small underpowered comparative studies suggested equivalence of either metronidazole or ciprofloxacin to sulfasalazine, methylprednisolone, and oral mesalamine (Pentasa). However, a placebo-controlled trial of metronidazole at 10 mg/kg daily or 20 mg/kg daily did not demonstrate efficacy in active Crohn's disease. Similarly, a comparative trial of budesonide 9 mg daily or combination therapy with budesonide 9 mg + metronidazole 1.5 g + ciprofloxacin 1.0 g daily did not demonstrate an adjunctive role for antibiotics in patients receiving budesonide therapy for active Crohn's disease. A single controlled trial of metronidazole, 1,500 mg daily for 3 months after ileal resection, showed that the occurrence of severe endoscopic lesions could be delayed for up to 1 year in patients undergoing an operation for Crohn's disease. Because of the results of these studies, the role of antibiotic therapy for Crohn's disease is debated. Many clinicians undertake a trial of antibiotic therapy before prescribing corticosteroids for active Crohn's disease.

Uncontrolled studies have reported that metronidazole, 750 to 1,500 mg daily, and ciprofloxacin, 1,000 mg daily, may be effective for fistulizing Crohn's disease, particularly in patients with 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.

Small placebo-controlled and comparative trials have shown that metronidazole, 750 to 1,500 mg daily, and ciprofloxacin, 1,000 mg daily, are effective for inducing remission in patients with active 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 vaginitis, anorexia, nausea, a metallic taste, and possible intolerance to alcohol. Adverse events observed with ciprofloxacin include photosensitivity, nausea, rash, increased levels of liver enzymes, and Achilles tendon rupture (rare). Ciprofloxacin should not be taken during pregnancy or breastfeeding, and metronidazole should be avoided during the first trimester of pregnancy.

CORTICOSTEROIDS

A small number of pharmacologic studies have been conducted with corticosteroids in inflammatory bowel disease, and they can be used to guide dosing and route of administration. A dose-response study in patients with active ulcerative colitis demonstrated that prednisone at doses of 40 or 60 mg daily is more effective than prednisone at 20 mg daily. More side effects occurred in the 60-mg daily dose group. These results have been extrapolated to patients with Crohn's disease. Most clinicians initiate oral corticosteroid therapy with prednisone at a dose of 40 mg daily and then taper the dose over 2 to 4 months. Pharmacokinetic studies in patients with active ulcerative colitis have demonstrated decreased bioavailability of prednisolone compared with that of controls. Thus, patients with severely active ulcerative colitis or Crohn's disease who do not have a response to oral corticosteroid therapy are hospitalized and given corticosteroids intravenously to ensure adequate bioavailability of the corticosteroid dose.

Placebo-controlled trials have demonstrated that orally administered cortisone, 100 mg daily, or prednisone, 40 to 60 mg daily, is effective for inducing remission in mildly to severely active ulcerative colitis. In contrast, placebo-controlled trials have shown that low-dose oral corticosteroid therapy (cortisone at 25 mg twice daily, prednisone at 15 mg daily, or prednisone at 40 mg every other day) is not effective for maintaining remission in ulcerative colitis.

No controlled trials of intravenous corticosteroid therapy for severely active ulcerative colitis have been conducted. Uncontrolled studies have suggested that intravenous prednisolone, 60 mg daily, or hydrocortisone, 300 to 400 mg daily, is effective for severely active ulcerative colitis. Most clinicians administer methylprednisolone, 40 to 60 mg daily, intravenously as a single bolus dose, in divided doses (2-4 times daily), or as a continuous infusion.

Placebo-controlled trials have demonstrated that hydrocortisone administered rectally as an enema at a dose of 100 mg daily or prednisolone at a dose of 5 mg daily is effective for inducing remission in mild to moderately active left-sided ulcerative colitis or ulcerative proctitis. Placebo-controlled trials also have shown that hydrocortisone enemas at a dose of 100 mg two nights per week are not effective for maintaining remission in left-sided ulcerative colitis or ulcerative proctitis.

Placebo-controlled trials have demonstrated that oral prednisone administered at a dose of 60 mg daily and 6-methylprednisolone at 48 mg daily are effective for inducing remission in mildly to moderately active Crohn's disease. In contrast, placebo-controlled trials have shown that low-dose corticosteroids (oral prednisone, 20 mg daily, or 6-methylprednisolone, 8 mg daily) are not effective for maintaining remission in Crohn's disease.

Both short-term and long-term adverse events occur frequently in patients receiving corticosteroid therapy. Short-term adverse events include 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. Corticosteroids may be taken during pregnancy and breastfeeding.

Budesonide is a newer corticosteroid, with 90% first-pass metabolism in the liver. It can be administered orally as a CIR formulation (release is pH dependent) or rectally as an enema. These "topical" formulations have fewer side effects than conventional corticosteroids. A placebo-controlled trial demonstrated that CIR budesonide at doses of 9 to 15 mg daily is effective for inducing remission in mild to moderately active ileal or right colonic Crohn's disease. Comparative studies have shown that oral CIR budesonide at 9 mg daily is more effective than mesalamine at 4 g daily and equivalent to oral corticosteroids for inducing remission in active Crohn's disease. In contrast, oral CIR budesonide at 3 mg daily is not effective for maintaining remission in Crohn's disease and 6 mg has only a modest short-term maintenance benefit.

AZATHIOPRINE AND 6-MERCAPTOPURINE

Azathioprine is a prodrug that, after being administered, is converted rapidly to 6-mercaptopurine. 6-Mercaptopurine, then, is either inactivated to 6-thiouric acid by xanthine oxidase or to 6-methylmercaptopurine by thiopurine methyltransferase, or it is activated through several enzyme steps to the 6-thioguanine nucleotides, which are thought to be the active metabolites. The enzyme activity of thiopurine methyltransferase is determined genetically: 1 in 300 patients have no enzyme activity, 10% have intermediate enzyme activity, and 90% have normal enzyme activity.

Placebo-controlled trials have demonstrated that azathioprine at doses of 1.5 to 2.5 mg/kg daily are effective for steroid-sparing in patients with steroid-dependent ulcerative colitis. Similarly, a placebo-controlled trial showed that azathioprine at 100 mg daily is effective for maintaining remission in ulcerative colitis, and another trial showed that azathioprine at 2.0 mg/kg daily was more effective than oral mesalamine at 3.2 g daily for this indication.

Placebo-controlled trials have demonstrated also that azathioprine at doses of 2 to 3 mg/kg daily and 6-mercaptopurine at a dose of 1.5 mg/kg daily are effective for inducing remission and closing fistulas in patients with active Crohn's disease. Similarly, placebo-controlled trials have shown that azathioprine at 2 to 3 mg/kg daily and 6-mercaptopurine at 1.5 mg/kg daily are effective

for maintaining remission in Crohn's disease and are steroid-sparing.

Adverse events that have been associated with azathioprine and 6-mercaptopurine include nausea, allergic reactions, pancreatitis, bone marrow suppression, drug hepatitis, and infectious complications. Patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine have approximately a fourfold increase in the risk of lymphoma. In selected cases, azathioprine and 6-mercaptopurine can be administered during pregnancy.

METHOTREXATE

A placebo-controlled trial demonstrated that methotrexate administered orally at a dose of 12.5 mg weekly is not effective for active ulcerative colitis or for maintaining remission.

Placebo-controlled trials have demonstrated that low-dose oral methotrexate, 12.5 mg weekly, is not effective for inducing or maintaining remission in Crohn's disease. In contrast, as shown by placebo-controlled trials, higher-dose methotrexate, 25 mg weekly given intramuscularly and possibly 15 mg weekly given orally, is effective for inducing remission in patients with steroid-dependent and steroid-refractory active Crohn's disease. A placebo-controlled trial also showed that methotrexate at doses of 15 to 25 mg weekly given intramuscularly is effective for maintenance of remission and steroid-sparing in Crohn's disease.

The adverse events that may occur with methotrexate therapy include rash, nausea, mucositis, diarrhea, bone marrow suppression, hypersensitivity pneumonitis, increased levels of liver enzymes, and liver fibrosis or cirrhosis. Methotrexate is contraindicated for pregnant women.

CYCLOSPORINE AND TACROLIMUS

A placebo-controlled trial of intravenous cyclosporine administered as a continuous infusion at a high dose of 4 mg/kg daily (equivalent to 12-16 mg/kg daily of oral cyclosporine) demonstrated efficacy for inducing remission in patients with severely active, steroid-refractory ulcerative colitis. A comparative trial showed that monotherapy with moderate-dose intravenous cyclosporine (2 mg/kg as a continuous daily infusion) has efficacy similar to that of high-dose intravenous cyclosporine (4 mg/kg as a continuous daily infusion) for inducing remission in patients with severely active ulcerative colitis. There are no controlled trials of oral cyclosporine for the treatment of active ulcerative colitis or for maintaining remission in ulcerative colitis. A placebo-controlled trial demonstrated that oral tacrolimus titrated to a target whole blood level of 10 to 15 ng/mL was more effective than placebo for inducing remission in patients with severely active, steroid-refractory ulcerative colitis.

Placebo-controlled trials of cyclosporine administered orally at a low dose of 5 mg/kg daily did not demonstrate efficacy for inducing remission in active Crohn's disease or for maintaining remission in Crohn's disease. There are no controlled trials of high-dose cyclosporine administered intravenously for severely active or fistulizing Crohn's disease.

A placebo-controlled trial of oral tacrolimus, 0.2 mg/kg daily, demonstrated efficacy for treatment of fistulizing Crohn's disease.

The adverse effects that may occur with cyclosporine therapy include headache, tremor, paresthesias, seizures, hypertrichosis, gingival hyperplasia, renal insufficiency, hypertension, infections, hepatotoxicity, nausea and vomiting, and anaphylaxis. The adverse effects that may occur with tacrolimus therapy include headache, tremor, paresthesias, renal insufficiency, hypertension, infections, and diabetes mellitus. Although not absolutely contraindicated, cyclosporine and tacrolimus therapy generally should be avoided for pregnant women.

INFLIXIMAB AND ADALIMUMAB

Infliximab is a chimeric IgG1 monoclonal antibody directed toward tumor necrosis factor (TNF)-α. Adalimumab is a fully human IgG1 monoclonal antibody directed toward TNF-α. Controlled trials have shown that infliximab at 5 mg/kg administered 3 times over 6 weeks as an intravenous infusion is effective for inducing remission and closing fistulas in active Crohn's disease and for inducing remission in patients with active ulcerative colitis. For patients who have a response to induction therapy with infliximab, re-treatment with infliximab at doses of 5 mg/kg or 10 mg/kg

administered intravenously every 8 weeks is effective for maintaining remission in Crohn's disease and ulcerative colitis and is steroid-sparing. Controlled trials have demonstrated that adalimumab administered subcutaneously at a dose of 160 mg at week 0 and 80 mg at week 2 is effective for inducing remission in active Crohn's disease, including in patients who previously had a response to infliximab therapy and then became intolerant or lost response to it. For patients who have had a response to adalimumab therapy, retreatment with it at a dose of 40 mg every other week or every week is effective for maintaining remission in Crohn's disease and is steroid-sparing and can result in fistula closure. Treatment of ulcerative colitis with adalimumab is investigational.

Adverse events that may occur with infliximab and adalimumab therapy include formation of human anti-chimeric antibodies (infliximab) or human anti-human antibodies (adalimumab), infusion reactions (infliximab), injection site reactions (adalimumab), delayed hypersensitivity reactions (infliximab), autoantibody formation, drug-induced lupus, infection (particularly tuberculosis and fungal infections such as histoplasmosis), and possibly non-Hodgkin's lymphoma. Human anti-chimeric antibodies frequently lead to higher rates of infusion reactions and loss of efficacy in patients receiving infliximab. The frequency of formation of human anti-chimeric antibodies in patients receiving infliximab is decreased when patients receive 1) three induction doses of infliximab, followed by systematic maintenance infusions every 8 weeks; 2) concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate; or 3) pretreatment with 200 mg of hydrocortisone administered intravenously. Human anti-human antibodies occur infrequently in patients receiving adalimumab when they are given a loading dose of adalimumab at weeks 0 and 2 and then systematic maintenance injections every 1 to 2 weeks. Although data are limited, infliximab and adalimumab can be prescribed for pregnant women in selected circumstances.

SURGERY FOR ULCERATIVE COLITIS

The original operation for ulcerative colitis consisted of total proctocolectomy with Brooke ileostomy (Fig. 1). In the 1970s, the continent ileostomy, or Kock pouch, served as an alternative to ileostomy (Fig. 1). Reoperation was frequently required with the Kock pouch. In the 1980s, the ileoanal pouch largely replaced the Kock pouch for patients with ulcerative colitis who required operation (Fig. 1). Colectomy is indicated for patients with ulcerative colitis who have definite low-grade or high-grade dysplasia, who have colorectal cancer, who are steroid-dependent, or who have disease refractory to medical therapy (including severely active steroid-refractory ulcerative colitis and toxic megacolon). Pouchitis is inflammation of the ileoanal pouch that leads to recurrent symptoms of diarrhea, urgency, and fecal incontinence. The cumulative frequency of acute pouchitis after colectomy with ileoanal pouch approaches 50% by 5 years. The frequency of chronic pouchitis is 5% to 10% by 5 years.

SURGERY FOR CROHN'S DISEASE

The probability of surgical resection in patients with Crohn's disease increases with time. By 15 years after diagnosis, 70% of patients have had at least one operation, and one-half of these have had two or more operations. In patients with extensive stricturing or numerous previous operations (or both), bowel-sparing techniques such as strictur-oplasty may be used (Fig. 2). In patients with perianal fistulas, incision and drainage of abscesses, fistulotomy, and placement of setons (drains) may be used in an attempt to avoid proctectomy.

TREATMENT STRATEGIES FOR ULCERATIVE COLITIS

Induction of Remission

Sulfasalazine, oral mesalamine, olsalazine, and balsalazide are effective for inducing remission in patients with active extensive or pancolonic ulcerative colitis. Patients with active ulcerative proctitis, ulcerative proctosigmoiditis, or left-sided ulcerative colitis may receive treatment with rectal mesalamine enemas or suppositories, corticosteroid enemas, the oral therapies outlined above for extensive and pancolonic ulcerative colitis, or a combination of oral and rectal therapy. For patients who have disease that is moderate to

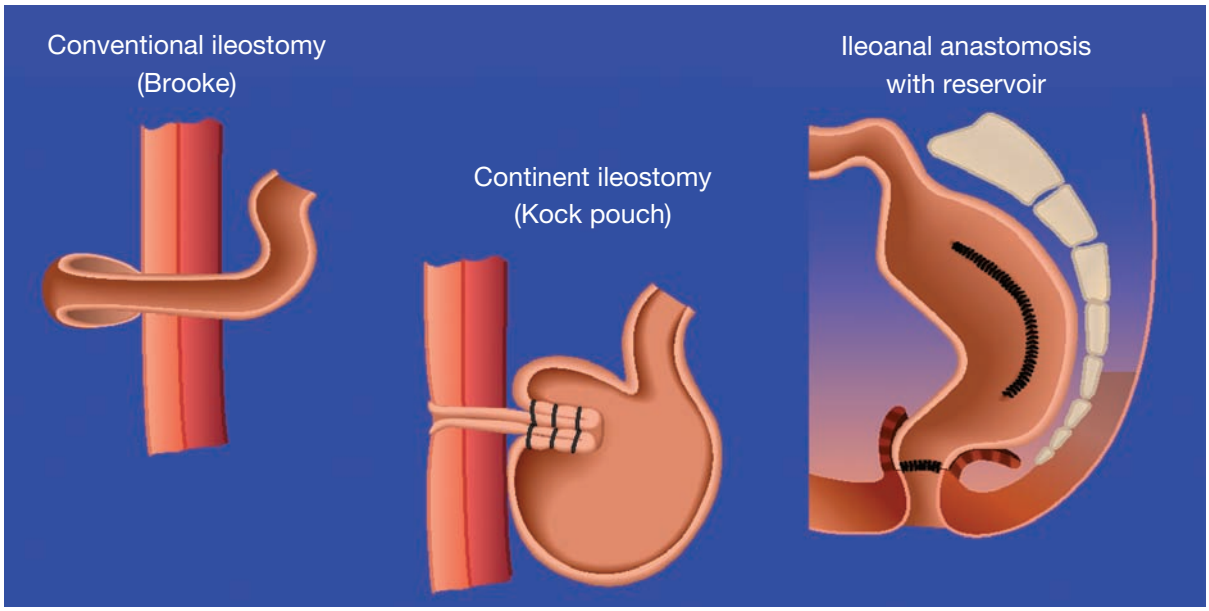

Fig. 1. Surgical options for ulcerative colitis.

severe and for patients for whom sulfasalazine, oral or rectal mesalamine, olsalazine, or balsalazide therapy failed, the next step is second-line therapy with prednisone. Patients with moderately active disease can receive oral prednisone as an outpatient. Patients who require corticosteroid therapy often become steroid dependent. Patients with persistent symptoms may require oral corticosteroids, azathioprine or 6-mercaptopurine, infliximab, or colectomy with ileostomy or ileoanal pouch. However, because of the slow onset of action, azathioprine and 6-mercaptopurine have limited use as induction agents in patients with significantly active ulcerative colitis. Infliximab is effective for the treatment of active ulcerative colitis refractory to other therapies, usually corticosteroids or immunosuppressive medications (or both). Patients who are more severely ill should be hospitalized for intravenous corticosteroid therapy, and if the disease does not respond, colectomy should be performed (intravenous cyclosporine, oral tacrolimus, and infliximab may be considered as alternatives to colectomy). Methotrexate is not effective for ulcerative colitis, and adalimumab is investigational for this condition.

Maintenance of Remission

Sulfasalazine, oral mesalamine, olsalazine, and balsalazide are effective for maintaining remission in patients with extensive or pancolonic ulcerative

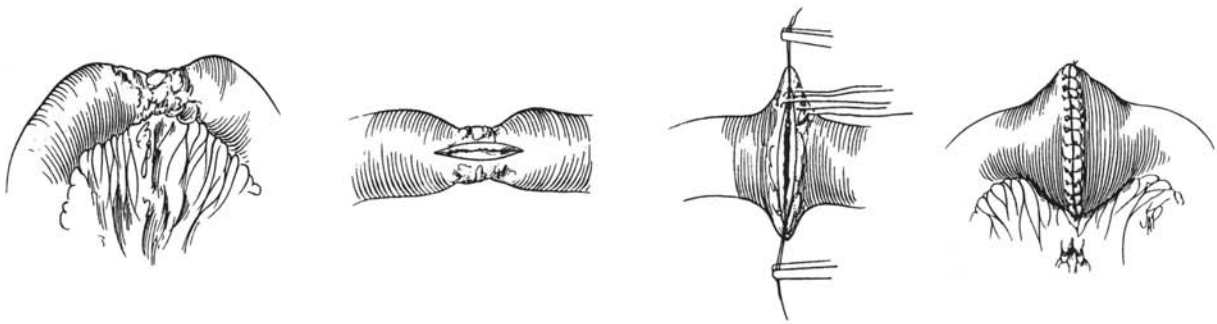

Fig. 2. Stricturoplasty for Crohn's disease.

colitis. Patients with ulcerative proctitis, ulcerative proctosigmoiditis, or left-sided ulcerative colitis can receive maintenance treatment with rectal mesalamine enemas or suppositories or with the oral therapies outlined above for extensive and pancolonic disease. Low-dose prednisone is not effective for maintaining remission, and patients who receive corticosteroid therapy for active ulcerative colitis often become steroid dependent. Azathioprine and 6-mercaptopurine are effective for maintaining remission, particularly steroid-induced remission, and for steroid-sparing. Infliximab is effective for maintaining remission in patients with disease refractory to other therapies. Administration of three induction doses over 6 weeks and then systematic maintenance dosing every 8 weeks and/or concomitant immunosuppression decreases the frequency of human anti-chimeric antibody formation. Methotrexate is not effective for ulcerative colitis, and adalimumab is investigational for this condition.

TREATMENT STRATEGIES FOR CROHN'S DISEASE

Induction of Remission

Sulfasalazine is modestly effective for inducing remission in patients with active Crohn's disease, with the benefit confined largely to patients with Crohn's colitis and ileocolitis. Mesalamine and metronidazole are not consistently effective for inducing remission. Nevertheless, many clinicians continue to prescribe these agents for inducing remission in patients with mild to moderately active Crohn's disease. Budesonide is more effective than mesalamine and similarly effective to but safer than prednisone. Thus, budesonide is the first-line treatment of choice for inducing remission in patients with mild to moderately active Crohn's disease that involves the terminal ileum or right colon, whereas sulfasalazine is the optimal first-line therapy for patients with Crohn's colitis. A traditional treatment algorithm for first-line therapy for Crohn's disease is shown in Figure 3. A newer evidence-based treatment algorithm for first-line therapy for Crohn's disease is shown in Figure 4.

For patients who have moderate to severe disease and for patients for whom budesonide or sulfasalazine therapy failed, the next step is second-line therapy with prednisone. Patients with moderately active disease can receive oral prednisone as outpatients, but more severely ill patients should be hospitalized for intravenous corticosteroid therapy. Often, patients who require corticosteroid therapy become steroid dependent. Because of the slow onset of action, azathioprine, 6-mercaptopurine, and methotrexate are of limited use as induction agents in patients with significantly active Crohn's disease. Infliximab and adalimumab are effective for the treatment of active Crohn's disease refractory to other therapies, usually corticosteroids or immunosuppressive medications (or both). Administration of three induction doses over 6 weeks and then systematic maintenance dosing every 8 weeks and/or concomitant immunosuppression reduces the frequency of human anti-chimeric antibody formation in patients receiving infliximab. Administration of two induction doses over 2 weeks and then systematic maintenance dosing every 1 to 2 weeks results in

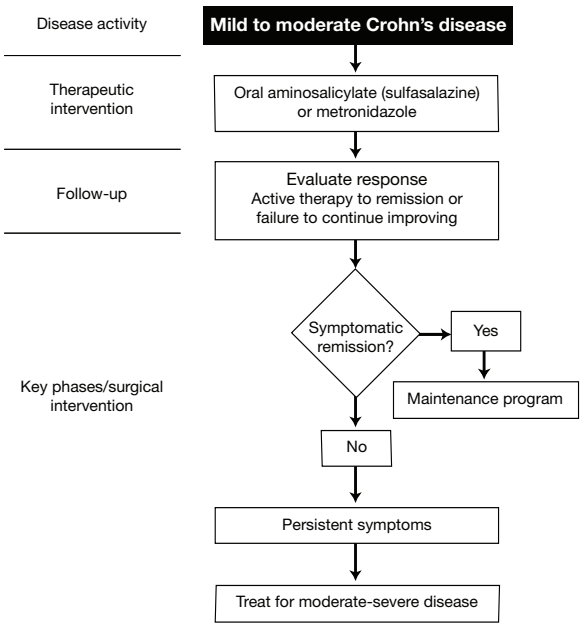

Fig. 3. Suggested treatment algorithm for mildly to moderately active Crohn's disease using the traditional approach to induction. (Modified from Sandborn WJ. Medical therapy for Crohn's disease. In: Sartor RB, Sandborn WJ, editors. Kirsner's inflammatory bowel diseases. 6th ed. Edinburgh: Saunders; 2004. p. 530-54. Used with permission.)

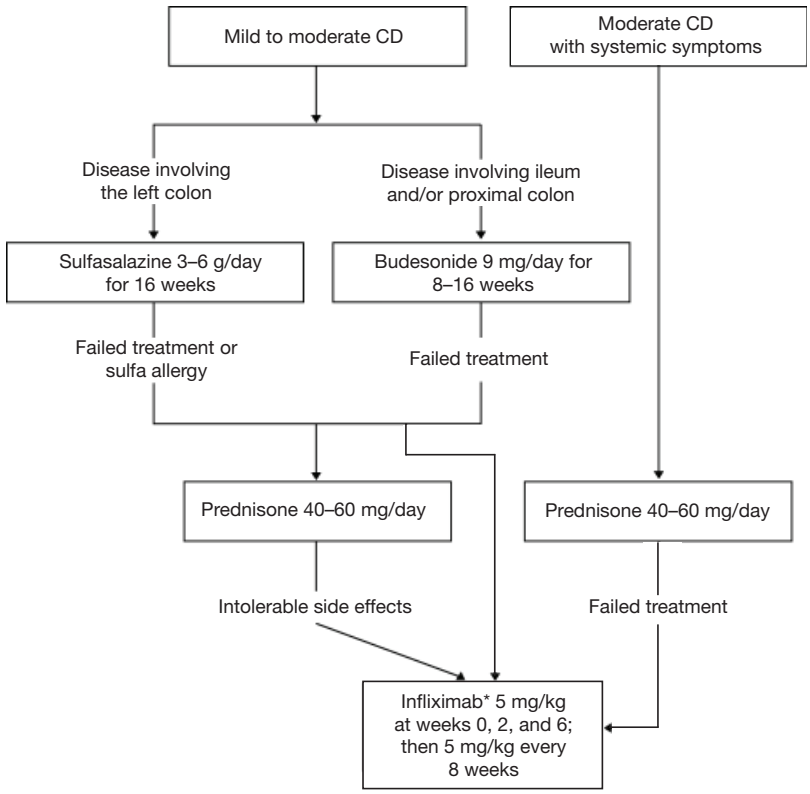

Fig. 4. Suggested treatment algorithm for mildly to moderately active Crohn's disease (CD), using an evidence-based approach. *Disease may need to be reclassified as moderate to severe. (From Sandborn WJ, Feagan BG, Lichtenstein GR. Medical management of mild to moderate Crohn's disease: evidence-based treatment algorithms for induction and maintenance of remission. Aliment Pharmacol Ther. 2007;26:987-1003. Used with permission.)

a low rate of human anti-human antibody formation in patients receiving adalimumab.

Maintenance Of Medically Induced Remission

Sulfasalazine is not effective for maintenance of medically induced remission, and mesalamine is not consistently effective. Metronidazole has not been evaluated for this indication. Low-dose prednisone is not effective for maintaining remission, and patients with active Crohn's disease treated with corticosteroids often become steroid dependent. Budesonide, 6 mg, prolongs the time to relapse, but a maintenance effect as defined by conventional criteria has not been demonstrated. Azathioprine, 6-mercaptopurine, and methotrexate are effective for maintaining remission, particularly corticosteroid-induced remission. Infliximab and adalimumab are effective for maintaining remission in patients with disease refractory to other therapies. Administration of three induction doses over 6 weeks and then systematic maintenance dosing every 8 weeks and/or concomitant immunosuppression decreases the frequency of human anti-chimeric antibody formation in patients receiving infliximab. Administration of two induction doses over 2 weeks and then systematic maintenance dosing every 1 to 2 weeks results in a low rate of human anti-human antibody formation in patients receiving adalimumab. A treatment algorithm for maintenance therapy in patients with Crohn's disease that is budesonide or prednisone dependent or refractory is shown in Figure 5.

Postoperative Maintenance of Remission

Sulfasalazine is not effective for postoperative maintenance of remission. Mesalamine is not

consistently effective and is of minimal benefit. Metronidazole, 20 mg/kg for 3 months, reduces the recurrence of severe endoscopic lesions at 3 months but does not alter clinical recurrence at 1 year, and adverse effects are common. Low-dose prednisone is not effective for postoperative maintenance therapy, nor is budesonide, 6 mg. Azathioprine and 6-mercaptopurine may be effective, but clinical data are sparse. In the absence of definitive data, these agents are currently the treatment of choice for patients who are deemed to be at "high risk" for recurrence. Methotrexate and infliximab have not been evaluated for postoperative maintenance of remission. A treatment algorithm for postoperative maintenance therapy for patients with Crohn's disease is shown in Figure 6.

Closure of Fistulas and Maintenance of Fistula Closure

Antibiotics may be effective for fistula closure, but no placebo-controlled trial has been performed. Similarly, azathioprine and 6-mercaptopurine may be effective for this treatment indication, but no controlled trials in which fistula closure is the primary end point have been conducted. Uncontrolled studies have suggested that cyclosporine may be effective. Controlled trials have not been performed. A placebo-controlled trial of tacrolimus did demonstrate effectiveness for fistula closure in patients with refractory fistulizing Crohn's disease. Infliximab and adalimumab are effective for both inducing and maintaining fistula closure. Currently, infliximab is the best evidence-based therapy for fistulas. Administration of a loading dose, followed by systematic maintenance therapy or concomitant immunosuppression (or both), is required. An algorithm for the treatment of perianal Crohn's disease is shown in Figure 7.

CONCLUSIONS

The conclusions regarding therapy for different treatment indications in patients with ulcerative colitis and Crohn's disease are summarized in Tables 2 and 3.

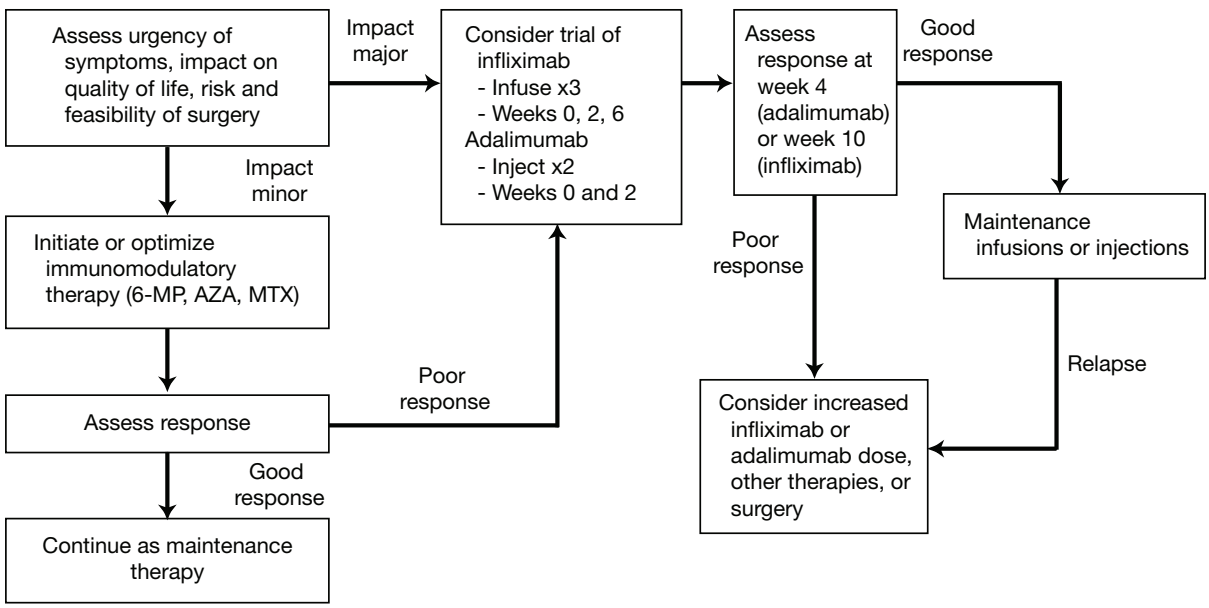

Fig. 5. Suggested treatment algorithm for managing patients with refractory Crohn's disease. AZA, azathioprine; 6-MP, 6-mercaptopurine; MTX, methotrexate. (Modified from Sands BE. Therapy of inflammatory bowel disease. Gastroenterology. 2000;118:S68-S82. Used with permission.)

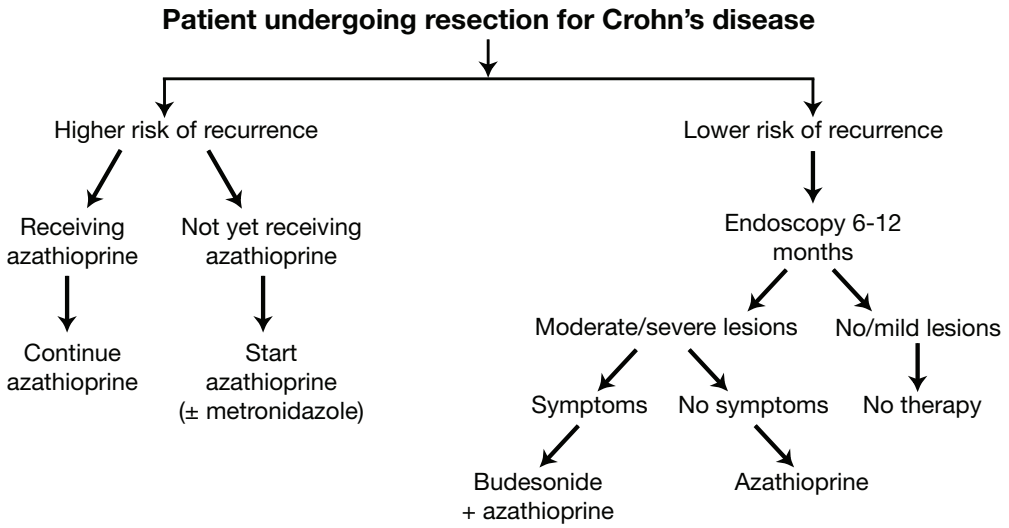

Fig. 6. Suggested treatment algorithm, using a new evidence-based approach, for approach to patients operated on for Crohn's disease. (From Sandborn WJ. Medical therapy for Crohn's disease. In: Sartor RB, Sandborn WJ, editors. Kirsner's inflammatory bowel diseases. 6th ed. Edinburgh: Saunders; 2004. p. 530-54. Used with permission.)

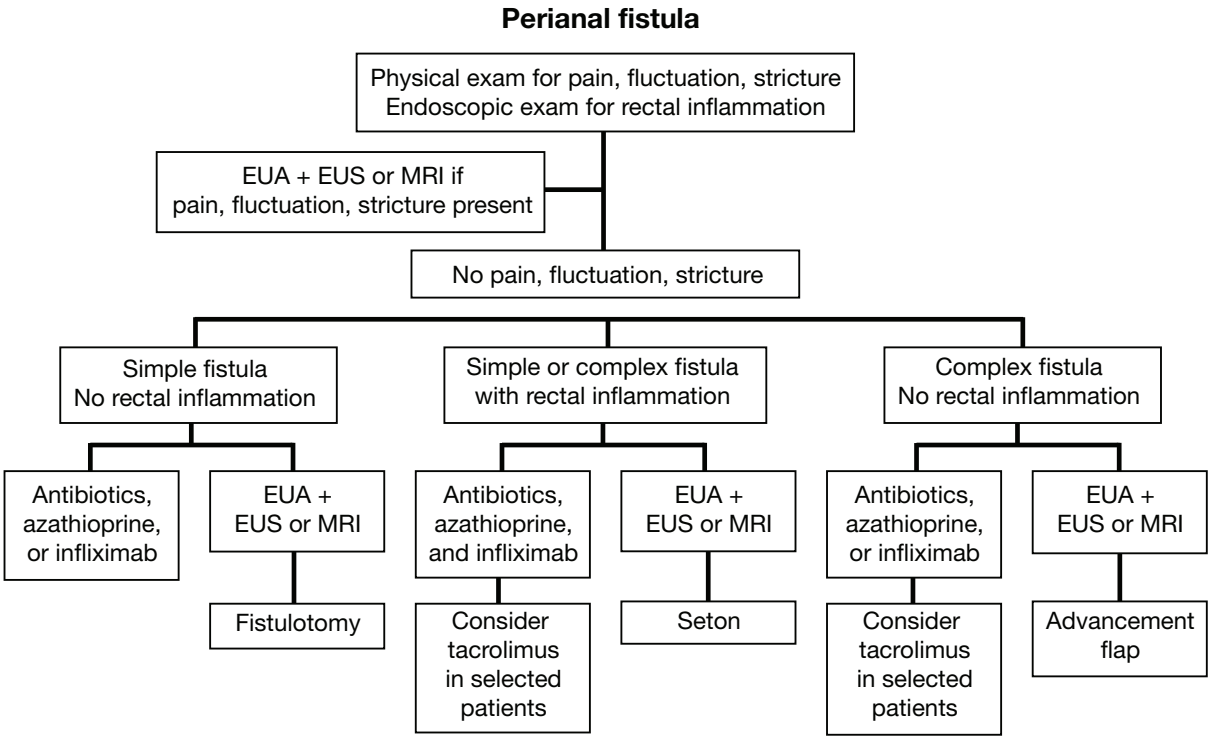

Fig. 7. Treatment algorithm for managing patients with Crohn's perianal fistulas. EUA, examination under anesthesia; EUS, anorectal endoscopic ultrasonography; MRI, pelvic magnetic resonance imaging. *Complex fistula* is high and/or has multiple external openings, perianal abscess, rectovaginal fistula, anorectal stricture, or macroscopic evidence of rectal inflammation. *Simple fistula* is low, has a single external opening, and does not have associated perianal abscess, rectovaginal fistula, anorectal stricture, or macroscopically evident rectal inflammation. (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;125:1508-30. Used with permission.)

Table 2. Ulcerative Colitis: Treatment According to Indication

	Mildly to moderately active				Remission maintenance	
Drug	**Distal**	**Extensive**	**Refractory**	**Severely active**	**Distal**	**Extensive**
Sulfasalazine	Yes	Yes	Yes*	No†	Yes	Yes
Rectal mesalamine	Yes	No	Yes*	No†	Yes	No
Oral mesalamine	Yes	Yes	Yes*	No†	Yes	Yes
Olsalazine	Yes	Yes	Yes*	No†	Yes	Yes
Balsalazide	Yes	Yes	Yes*	No†	Yes	Yes
Rectal corticosteroids	Yes	No	Yes*	Yes‡	No	No
Oral corticosteroids	Yes	Yes	Yes*	No	No	No
Intravenous corticosteroids	No	No	Yes§	Yes	No	No
Azathioprine /6-mercaptopurine	No	No	Yes	No	Yes	Yes
Cyclosporine	No	No	No	Yes	No	No
Tacrolimus	No	No	No	Yes	No	No
Infliximab	No	No	Yes	Yes	Yes	Yes
Colectomy	No	No	Yes	Yes	No	No

**Typically continued as a carryover of treatment for mild to moderately active disease when additional agents are added.*
†Typically discontinued because of the possibility of intolerance to sulfasalazine, mesalamine, or balsalazide.
‡Adjunctive therapy to intravenous corticosteroids.
§Some patients in whom therapy with oral corticosteroids has failed will have a response to hospitalization with intravenous administration of corticosteroids.

Table 3. Crohn's Disease: Treatment According to Indication

Drug	Mildly to moderately active	Refractory	Fistulizing	Severely active	Remission maintenance
Sulfasalazine	Yes	?Yes*	No	No†	?Yes‡
Oral mesalamine	?Yes‡	?Yes*	No	No†	?Yes‡
Antibiotics	?Yes‡	?Yes*	?Yes‡	No	?Yes‡
Budesonide	Yes	?Yes*	No	No	No
Oral corticosteroids	Yes	Yes*	No	No	No
Intravenous corticosteroids	No	Yes§	No	Yes	No
Azathioprine/6-mercaptopurine	No	Yes	Yes	No	Yes
Methotrexate	No	Yes	No	No	Yes
Cyclosporine	No	No	?Yes//	?Yes//	No
Tacrolimus	No	No	Yes	No	No
Infliximab	No	Yes	Yes	?Yes	?Yes
Adalimumab	No	Yes	Yes	Yes	Yes
Surgical resection	No	Yes	Yes	Yes	No

**Controlled trials do not show an adjunctive benefit for sulfasalazine, mesalamine, or antibiotics when combined with corticosteroids or budesonide. Typically continued as a carryover of treatment for mildly to moderately active disease when additional agents are added.*

†Typically discontinued because of the possibility of intolerance to sulfasalazine or mesalamine.

‡Controlled trials do not uniformly show benefit, but treatment commonly is used in clinical practice.

§Some patients in whom therapy with oral corticosteroids has failed will have a response to hospitalization with intravenous administration of corticosteroids.

//No controlled trials conducted; uncontrolled studies suggest benefit.

RECOMMENDED READING

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CHAPTER 16

Inflammatory Bowel Disease: Extraintestinal Manifestations and Cancer

Edward V. Loftus, Jr., MD

Although ulcerative colitis and Crohn's disease are idiopathic inflammatory bowel diseases (IBDs) that by definition affect the gastrointestinal tract, they are associated with a wide variety of systemic complications. Classically, such extraintestinal manifestations are defined as immune-mediated phenomena that affect the joints, eye, skin, or hepatobiliary tract, but they can be defined more broadly to include complications in other organ systems and complications that arise as a direct pathophysiologic consequence of extensive bowel inflammation or resection. This chapter reviews the most common extraintestinal manifestations, their relationship to activity of the underlying bowel disease, and their treatment.

One of the complications of IBD most feared by patients and physicians alike is the development of colorectal cancer. IBD is associated less commonly with other malignancies, such as cholangiocarcinoma. The risk of colorectal cancer may be mitigated partially with colonoscopic surveillance. This chapter reviews risk factors for cancer and provides an algorithm for surveillance colonoscopy.

ARTHRITIS

The overall prevalence of IBD-related rheumatologic manifestations is thought to be approximately 30%. Several types of arthritis have been identified, each with its own clinical presentation, natural history, and treatment (Table 1).

Arthritis affecting the axial skeleton can be classified into the more common, frequently asymptomatic, sacroiliitis and the less common, more progressive, ankylosing spondylitis. Subtle inflammatory changes of the sacroiliac joints may be detected with magnetic resonance imaging in up to 45% of patients with IBD, but most patients are asymptomatic. Typical changes seen on plain radiographs of the sacroiliac joints include narrowing of the joints and surrounding sclerosis. Symptomatic sacroiliitis manifests as low back pain and stiffness, typically worse in the morning and with rest. A subset progresses to ankylosing spondylitis, which involves the vertebral facet joints and associated ligaments, resulting in progressive stiffness and lordosis of the spine. The prevalence of ankylosing spondylitis in IBD ranges between 1% and 6% across studies, with a higher prevalence in

Abbreviations: IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

Table 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)

Crohn's disease than in ulcerative colitis. The relationship between spondyloarthropathy, intestinal inflammation, and classic IBD is complex. Many patients with ankylosing spondylitis who have no gastrointestinal symptoms have evidence of subtle ileal inflammation, and symptomatic Crohn's disease eventually develops in 5% to 10% of these patients. Radiographic changes of ankylosing spondylitis include squaring of the vertebral bodies in the early stages, followed by the classic "bamboo spine" appearance of syndesmophytes between the vertebral bodies. The HLA-B27 antigen is associated with ankylosing spondylitis in 50% to 75% of patients who have concomitant IBD and ankylosing spondylitis. HLA-B27 positivity in patients with sacroiliitis implies a higher risk of progression to ankylosing spondylitis.

The clinical course of the axial arthritides associated with IBD appears to be unrelated to the activity of the underlying bowel disease. The course of ankylosing spondylitis is typically progressive even if the associated IBD is quiescent. The treatment of ankylosing spondylitis has been revolutionized with the availability of tumor necrosis factor (TNF) antagonists. First-line therapy consists of physical therapy directed at maintaining spinal mobility, analgesics such as acetaminophen (with or without mild opioid agents such as propoxyphene or hydrocodone), and antiinflammatory agents if needed. Conventional nonsteroidal antiinflammatory drugs can be a problem because they may trigger an exacerbation of IBD. There is little evidence that methotrexate is effective in treating ankylosing spondylitis. In more resistant cases, etanercept, infliximab, or adalimumab is indicated.

The peripheral arthritis that occurs with IBD consists of two subtypes that are associated with different HLA antigens. Type 1, the more common type, is an asymmetric oligoarticular arthritis that affects primarily large joints such as the knees, ankles, wrists, and elbows. The clinical presentation consists of joint pain and swelling, with limited range of motion. Plain radiographs typically do not show destructive changes, although they rarely may be apparent. Type 1 arthritis is usually self-limited, and its activity mirrors the activity of the underlying IBD. Rarely, this form of peripheral arthritis becomes more chronic. Type 2 arthritis is a more chronic symmetric polyarthritis, similar to rheumatoid arthritis; however, rheumatoid factor is typically absent. The activity of this arthritis is independent of the associated IBD. Initial treatment of peripheral arthritis consists of physical therapy and analgesics. Nonsteroidal antiinflammatory drugs may exacerbate the underlying IBD. Sulfasalazine should be considered the aminosalicylate of choice because it has mild efficacy for symptoms of peripheral arthritis. Corticosteroids, administered by either oral ingestion or intra-articular injection, may be required. Considerable evidence supports the use of methotrexate for treating peripheral manifestations of spondyloarthropathy in patients with IBD. For refractory cases of peripheral arthritis, an anti-TNF agent may be required.

OCULAR MANIFESTATIONS

Inflammatory ocular complications occur in 1% to 13% of patients with IBD (Table 2). The most common forms are anterior uveitis (also known as iritis) and scleritis. An inflammatory retinopathy or keratitis (corneal inflammation) may occur less frequently. Anterior uveitis occurs in up to 6% of patients with IBD and manifests with ocular pain, redness, photophobia, or blurred vision. The presentation may be either acute or chronic. The acute form is associated with HLA-B27 in 50% of patients; the chronic form is not associated with any particular HLA antigen. If the diagnosis is suspected, it

Table 2. Ocular Manifestations of Inflammatory Bowel Disease

Inflammatory
Anterior uveitis (iritis)
Scleritis
Episcleritis
Retinitis (rare)
Treatment-related (corticosteroids)
Cataracts
Glaucoma

should be confirmed with a slit-lamp examination by an ophthalmologist. (Indeed, any ocular symptoms in a patient with IBD should prompt referral to an ophthalmologist.) The activity of the HLA-B27–associated form does not necessarily correlate with the activity of the IBD, whereas the activity of the chronic form unrelated to HLA antigens typically mirrors the activity of the bowel disease. A recent retrospective study suggested that sulfasalazine treatment caused fewer exacerbations of uveitis in the year after therapy was initiated than during the previous year (from 3.4 to 0.9 flares per year). If left untreated, uveitis can result in irreversible complications such as adhesions, cataracts, and glaucoma. Initial treatment consists of topical corticosteroids and cycloplegic agents. For more refractory disease, oral corticosteroids may be required. Recent studies have shown the steroid-sparing qualities of methotrexate in this setting, and the results of open-label studies of TNF inhibitors for the treatment of uveitis have been promising.

Episcleritis and scleritis produce symptoms of eye irritation (eg, burning and itching) and conjunctival erythema. The activity of these conditions typically correlates with the activity of the IBD. Initial treatment consists of topical corticosteroids, but oral corticosteroids may be required for refractory scleritis. Again, because an untrained physician cannot differentiate vision-threatening conditions such as scleritis from nonthreatening conditions such as episcleritis, ocular symptoms in a patient with IBD should prompt referral to an ophthalmologist.

Some ocular complications may be treatment-related (Table 2). The most common example is cataract formation after prolonged treatment with corticosteroids. The cumulative incidence of cataract formation may be as high as 85% after 4 years of corticosteroid use. Less commonly, prolonged corticosteroid therapy may precipitate the development of glaucoma. Patients with IBD who have required prolonged courses of corticosteroids (ie, several years) should have periodic eye examinations even if they are asymptomatic.

DERMATOLOGIC MANIFESTATIONS

The two most common dermatologic extraintestinal manifestations are pyoderma gangrenosum and erythema nodosum. However, numerous other disorders of the skin have been described in association with IBD (Table 3). Pyoderma gangrenosum is an idiopathic ulcerative skin disease that occurs in up to 12% of patients with IBD. It is manifested initially as a pustular lesion, which evolves to an ulcer with undermining borders. The lesion often exhibits "pathergy," or a tendency to worsen with trauma. The most common location is the lower extremity, but the lesion can occur anywhere, including peristomal areas in patients with ostomies. Although skin biopsy findings may be helpful in excluding other conditions, pyoderma gangrenosum has no pathognomonic histologic features, and the diagnosis is a clinical one. Bacterial and fungal superinfection should be

Table 3. Dermatologic Manifestations of Inflammatory Bowel Disease

Common
Pyoderma gangrenosum
Erythema nodosum
Cutaneous ("metastatic") Crohn's disease
Aphthous stomatitis
Less common
Bowel-associated dermatosis-arthritis syndrome (bowel bypass syndrome)
Sweet's syndrome (acute neutrophilic dermatosis)
Epidermolysis bullosa acquisita
Mucosal cobblestoning of buccal mucosa and palate
Pyostomatitis vegetans

excluded. The course of pyoderma gangrenosum is independent of the associated IBD. First-line treatment consists of oral corticosteroids. There should be a low threshold for institution of immunosuppressive therapies so that the dose of corticosteroids can be tapered rapidly. The most commonly used immunosuppressive agents are cyclosporine and tacrolimus, although azathioprine and mycophenolate mofetil have been used occasionally for more chronic lesions. Case reports and case series have reported the efficacy of infliximab in both adult and pediatric patients with refractory pyoderma gangrenosum.

Erythema nodosum occurs more commonly in Crohn's disease (up to 15% of cases) but may occur rarely in ulcerative colitis (up to 5% of cases). For reasons that are unclear, this complication is most likely to develop in young women. The presentation is painful, tender, erythematous subcutaneous nodules, most typically in the pretibial areas. The activity of erythema nodosum tends to correlate with that of the underlying IBD, and the lesions typically resolve with aggressive treatment of the bowel disease. Supportive care for erythema nodosum includes leg elevation, support stockings, bed rest, and nonsteroidal antiinflammatory drugs. *Cutaneous Crohn's disease* refers to granulomatous lesions of the skin, most commonly in the perianal region. When such changes occur distant to the perineum, they are sometimes called *metastatic Crohn's disease*. These lesions occur as erythematous plaques or nodules. Disease activity may not correlate with that of the underlying IBD, and treatment may be difficult. Corticosteroids and immunosuppressive therapy frequently are required.

Oral manifestations of inflammatory bowel disease include oral aphthous ulcers (which occur in up to 10% of patients with Crohn's disease) and, less commonly, mucosal cobblestoning of the buccal mucosa and palate and pyostomatitis vegetans. The latter is characterized by pustules, erosions, and plaques on the buccal and gingival mucosa.

HEPATOBILIARY MANIFESTATIONS

The most important hepatobiliary condition associated with IBD is primary sclerosing cholangitis (Table 4). This idiopathic chronic cholestatic liver disease is characterized by inflammation and fibrosis of the biliary tree. Approximately 75% to 80% of all patients with primary sclerosing cholangitis have associated IBD, and most of these have ulcerative colitis. Conversely, 2% to 7% of patients with ulcerative colitis and an even smaller percentage of patients with Crohn's disease have associated primary sclerosing cholangitis. Patients present with pruritus and jaundice in advanced stages of the condition; however, with increased diagnostic awareness, the most frequent presentation is in an asymptomatic patient with IBD who has abnormal results on liver biochemistry tests. The presence of numerous strictures and dilatations of the extrahepatic or intrahepatic biliary tree found on endoscopic retrograde cholangiopancreatography most commonly confirms the diagnosis. Liver biopsy may be necessary for diagnosis in small duct primary sclerosing cholangitis (formerly known as "pericholangitis"). The IBD associated with primary sclerosing cholangitis is commonly mild in activity and almost always pancolonic in extent. Rectal sparing and "backwash ileitis" appear to be more common in primary sclerosing cholangitis-related IBD than in typical ulcerative colitis, suggesting that primary sclerosing cholangitis-associated IBD may be a unique phenotype. The course of primary sclerosing cholangitis is completely independent of the underlying IBD, and even total proctocolectomy is thought to have no effect on its natural history. The disease course is typically progressive, and there are no proven

Table 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)

medical therapies, although high-dose ursodeoxycholic acid appears promising. Orthotopic liver transplantation may be required. Complications include acute cholangitis, formation of dominant biliary strictures, choledocholithiasis, and cholangiocarcinoma (see Chapter 29, Cholestatic Liver Disease).

Autoimmune hepatitis is associated rarely with IBD, but when it is, it usually is associated with ulcerative colitis. Some patients may have features of both autoimmune hepatitis and primary sclerosing cholangitis (the so-called overlap syndrome) (see Chapter 31, Autoimmune Hepatitis).

Cholelithiasis is a common consequence of Crohn's disease. Either inflammation or surgical resection of the distal ileum impairs enterohepatic recycling of bile salts and upsets the balance of bile salts, cholesterol, and phospholipids, leading to an increased tendency to form cholesterol crystals and stones. Pigment stones also have been implicated in patients with steatorrhea, most likely because of impaired enterohepatic circulation of bilirubin.

OSTEOPENIA AND OSTEOPOROSIS

Accumulating evidence strongly suggests that osteopenia and osteoporosis are highly prevalent in IBD (up to 50%-70% of patients, depending on the patients studied and definitions used) (Table 1). Several factors may have a role, including corticosteroid use, malabsorption of calcium and vitamin D, malnutrition, low body mass index, cigarette smoking, and increased concentrations of cytokines, which contribute to bone resorption. However, conventional risk factors for osteoporosis such as female sex, menopause, and increasing age are equally important in patients with IBD. Although corticosteroid use is thought by some investigators to be the most important risk factor for osteoporosis in IBD, vertebral compression fractures have been diagnosed occasionally in patients with IBD who have never received corticosteroids. Bone loss associated with corticosteroid use is rapid, and the bulk of the loss occurs within the first several months of therapy. Unexpectedly, population-based studies of patients with IBD have shown only a modestly increased risk of actual bone fracture compared with that of the general population. The diagnosis of osteoporosis is made with bone mineral densitometry (dual photon absorptiometry). A T score of –2.5 (more than 2.5 standard deviations below mean bone mass for a young adult) signifies osteoporosis, and a T score between –1 and –2.5 signifies osteopenia. There is as yet no consensus about which patients with IBD should have densitometry screening. Patients with IBD who have the usual risk factors, including the postmenopausal state and low body mass index, should have the screening test. Also, patients whose cumulative systemic corticosteroid exposure is more than 6 months should be considered for testing. Treatment consists of calcium and vitamin D supplementation (1,200 mg calcium and 800 IU vitamin D), sex hormone replacement if deficient, and an oral bisphosphonate (alendronate, risedronate, or ibandronate). For patients who are intolerant of oral bisphosphonates, therapeutic options include intravenous bisphosphonates (pamidronate, zoledronic acid, or ibandronate) intranasal calcitonin, or parenteral teriparatide.

MISCELLANEOUS COMPLICATIONS

Renal complications are most common in Crohn's disease (Table 5). Nephrolithiasis may occur in up to 10% of patients with Crohn's disease, mostly a result of calcium oxalate stone formation. Intestinal inflammation or resection cause excessive absorption of oxalate. With fat malabsorption, the intestinal luminal calcium, which normally binds to oxalate, binds instead to fatty acids, leaving oxalate free to be absorbed from the colonic lumen. Patients with ulcerative colitis, especially those who have had colectomy, have a slightly increased tendency to form uric acid stones. Other renal complications include glomerulonephritis, right ureteral obstruction due to ileal inflammation, and enterovesical fistula formation. Interstitial nephritis can result from an idiosyncratic reaction to 5-aminosalicylate products, and it is recommended that renal function be assessed at baseline and monitored periodically thereafter.

Hematologic complications such as anemia, thrombocytosis, and leukocytosis are common. Anemia may be multifactorial (eg, iron or vitamin B_{12} deficiency and anemia of chronic disease), and, rarely, it is a sign of an associated hematologic disorder such as autoimmune hemolytic anemia, myelodysplastic syndrome, or promyelocytic leukemia.

Table 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)
  - Tubulointersitial nephritis (5-aminosalicylates)
- 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
  - Bronchiolitis obliterans with organizing pneumonia
- Pancreatic
  - Acute pancreatitis
    - Drug-induced (purine analogues, 5-aminosalicylates)
    - Duodenal Crohn's disease
    - Granulomatous involvement of pancreas (rare)
  - Chronic pancreatitis
    - Autoimmune pancreatitis
- Thrombophilia
  - Multifactorial

Various cardiopulmonary complications have been described, including pericarditis, myocarditis, conduction abnormalities, eosinophilic pneumonia, and interstitial pneumonitis. Pericarditis and pneumonitis may arise both as a true extraintestinal manifestation and as an allergic complication of treatment with sulfasalazine or other 5-aminosalicylates.

In IBD, pancreatitis most commonly occurs as a complication of medical therapy. Azathioprine and 6-mercaptopurine are most likely to result in pancreatitis (3%-5% of patients). Also, but rarely, acute pancreatitis has developed after treatment with sulfasalazine or other 5-aminosalicylates. In patients with duodenal Crohn's disease, pancreatitis may result from a stricture or fistula formation. However, up to 50% of patients with IBD have no obvious cause of pancreatitis, and a subset of these may have a true extraintestinal manifestation. In some patients with Crohn's disease, granulomatous inflammation of the pancreas seems to develop. Furthermore, antipancreatic antibodies have been described in up to 30% of patients with Crohn's disease.

Thromboembolism is more common in patients with IBD than in the general population, probably because of various factors. Activation of the inflammatory cascade in IBD appears to result in secondary activation of important mediators of thrombosis, such as platelets, fibrinogen, and fibrinopeptide A. A single genetic mutation does not appear to be responsible, but cases of factor V Leiden mutation, protein C deficiency, and protein S deficiency have been described. Initially, the risk of thromboembolism was tied to the activity of IBD, but there are numerous reports of thromboembolic activity in the absence of active IBD.

COLORECTAL CANCER

Patients with ulcerative colitis, and likely Crohn's colitis, are at increased risk for colorectal cancer, and this remains an important cause of mortality in patients with IBD. In most population-based studies of ulcerative colitis, the relative risk of colorectal cancer is 2 to 8 times higher than that of the general population. Overall, the absolute risk, or cumulative incidence, of colorectal cancer is 8% to 18% after 20 to 30 years of ulcerative colitis. However, when the risk is stratified by the extent of disease, it is clear that more extensive disease confers a higher risk of colorectal cancer (Table 6). The cumulative incidence of colorectal cancer among patients with extensive ulcerative colitis (ie, extent of disease proximal to the splenic flexure) ranges from 6% to 50% after 30 years of disease.

Another major risk factor appears to be duration of ulcerative colitis. The cumulative risk of colorectal cancer does not seem to be higher than that for the general population until 8 to 10 years after diagnosis, and the increase in risk is 0.5% to 1% each year thereafter. Whether age at onset of colitis is a risk factor independent of disease duration is unclear.

Another important risk factor for colorectal cancer in IBD appears to be the presence of primary sclerosing cholangitis. Whether primary sclerosing cholangitis is a truly independent risk factor for colorectal cancer or whether it functions as a marker for long-standing but asymptomatic pancolitis is not clear. Also, a family history of colorectal cancer in a patient with IBD appears to be a risk factor for cancer independent of the aforementioned factors.

In many studies, prolonged treatment with 5-aminosalicylates or sulfasalazine appears to decrease the risk of colorectal cancer substantially. Conversely, in the period when non-sulfonamide 5-aminosalicylate agents were not available commercially, the presence of sulfonamide allergy appeared to be a risk factor for colorectal cancer. However, the data are conflicting on this point, in that some studies have not found a risk reduction for patients receiving treatment with 5-aminosalicylates. Several studies also have suggested that the use of ursodeoxycholic acid is associated with a lower risk of colorectal neoplasia among patients with primary sclerosing cholangitis who have IBD.

Dysplasia frequently precedes or is associated with IBD-related colorectal cancer. The dysplastic change may be flat or polypoid on endoscopy. Surveillance colonoscopy with biopsy at regular intervals is offered to many patients with long-standing and extensive ulcerative colitis in an attempt to manage the increased risk of colorectal cancer. Although surveillance colonoscopy has never been proved to decrease colorectal cancer-related mortality of patients with IBD, several retrospective studies have suggested this to be the case. Surveillance is thought to detect early, curable cancers and to identify patients at increased risk for the development of cancer. The use of staining dyes in combination with high-magnification lenses (also known as *chromoendoscopy*) may increase substantially the ability of the endoscopist to detect dysplastic lesions. This technique is actively being studied.

Table 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 noncompliance or lack of follow-up
No or minimal use of sulfasalazine or 5-aminosalicylates
Sulfonamide allergy

We recommend institution of regular surveillance colonoscopy with biopsy after 8 to 10 years of left-sided or extensive colitis in both ulcerative colitis and Crohn's disease. This procedure should be performed at least every other year, and some experts advocate yearly procedures. Patients with only proctitis do not have an increased risk of colorectal cancer and do not require surveillance colonoscopy. Patients with primary sclerosing cholangitis should begin surveillance colonoscopy immediately. Random biopsy specimens should be obtained in a consistent fashion ("the more biopsies, the better"). Some experts advocate four-quadrant biopsies every 10 to 15 cm, which results in approximately 40 biopsy specimens. At Mayo Clinic, we obtain a minimum of 32 biopsy specimens (4 each from the cecum, ascending, proximal transverse, distal transverse, proximal descending, distal descending, and sigmoid colon and rectum). These are placed in four bottles (eight per bottle). In addition to the 32 random samples, specimens are obtained from suspicious lesions or nodules and placed in separate bottles.

Most investigators agree that patients with flat, high-grade dysplasia are at particularly high risk for either synchronous cancer or metachronous cancer in the near future. Immediate colectomy is recommended. However, debate continues about whether patients with flat, low-grade dysplasia should be offered immediate colectomy or more intensive surveillance colonoscopy. At Mayo Clinic, we recommend immediate colectomy because most retrospective studies have suggested that the 5-year risk for progression to high-grade dysplasia, polypoid dysplasia, or cancer after a diagnosis of low-grade dysplasia may be as high as

50%. The management of polypoid dysplasia (formerly known as dysplasia-associated lesion or mass) also is evolving. Previous dogma suggested that all such lesions were an indication for immediate colectomy. However, recent studies have suggested that if these lesions are not associated with flat dysplasia in the surrounding mucosa, they can be removed safely with colonoscopic polypectomy and then followed up closely.

OTHER CANCERS

Patients with ulcerative colitis are at increased risk for cholangiocarcinoma, likely because of the increased risk of primary sclerosing cholangitis in the population with ulcerative colitis. (Primary sclerosing cholangitis is a risk factor for cholangiocarcinoma.) Patients who have Crohn's disease with small-bowel involvement seem to be at increased risk for small-bowel adenocarcinoma compared with the general population. However, the absolute risk is low, and surveillance for this lesion is not recommended. Whether IBD is a risk factor for lymphoma is a matter of controversy. Population-based studies generally have not shown an increased relative risk, although this has been suggested by several referral center-based studies. The question has become more complicated with widespread use of immunosuppressive agents such as azathioprine, 6-mercaptopurine, methotrexate, and infliximab. It is well recognized that immunosuppressed states, such as posttransplantation state and acquired immunodeficiency syndrome, are associated with an increased risk of lymphoproliferative disorders. Although most individual studies of patients with IBD who have received immunosuppressive agents have not shown an increased risk of lymphoma, a meta-analysis of lymphoma risk among patients with IBD being treated with 6-mercaptopurine or azathioprine suggested a threefold increase in lymphoma risk. It is important to emphasize that the absolute risk of lymphoma is small, and, in most situations, the benefits of the drug outweigh this potential risk.

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CHAPTER 17

Gastrointestinal Infections, *Clostridium difficile*-Associated Disease, and Diverticular Disease

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Infections are a common cause of gastrointestinal disease. This chapter focuses on the more common infectious causes of diarrhea, food poisoning, and diverticulitis. It does not review *Helicobacter pylori* infection, bacterial overgrowth, or infections in patients seropositive for human immunodeficiency virus (HIV), because they 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 one 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 (Table 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 2).

VIRUSES

In the United States, most cases of gastroenteritis are viral and usually are brief and self-limited (Table 3). Viral gastroenteritis usually is characterized by diarrhea of brief duration, often with nausea and vomiting, but 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

Abbreviations: AIDS, acquired immunodeficiency syndrome; EAEC, enteroaggregative E. coli*; EHEC, enterohemorrhagic* E. coli*; EIEC, enteroinvasive* E. coli*; ELISA, enzyme-linked immunosorbent assay; EPEC, enteropathogenic* E. coli*; ETEC, enterotoxigenic* E. coli*; HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; TMP-SMX, trimethoprim-sulfamethoxazole; TTP, thrombotic thrombocytopenic purpura.*

Table 1. Effectiveness of Antibiotic Therapy for Infectious Diarrhea

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 cholerae
Giardia
Amebiasis
Antibiotics are possibly effective
Enteroinvasive *Escherichia coli*
Enteropathogenic *Escherichia coli*
Campylobacter enteritis
Vibrio parahaemolyticus
Antibiotics probably are not effective
Enterohemorrhagic *Escherichia coli* (including O157:H7)
Salmonella enterocolitis
Yersinia enteritis without sepsis
Mild-to-moderate traveler's diarrhea

Modified from Banerjee S, LaMont JT. Treatment of gastrointestinal infections. Gastroenterology. 2000;118 Suppl 1:S48-S67. Used with permission.

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 severe small-bowel infection. Treatment focuses on dehydration. Oral rehydration is optimal because oral nutrition stimulates mucosal repair, leading to shorter duration and less severe diarrhea. Protective immunity may not develop after natural infections, although reinfection tends to be less severe. An effective vaccine was developed but was withdrawn because of an association with intussusception.

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 caliciviruses are the Norwalk-like viruses. Outbreaks are associated with contaminated food (eg, shellfish), water, or 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 common, although usually less severe 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.

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 have bloody diarrhea, high fever or pain, fecal leukocytes, immunocompromise, 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.

Many bacterial causes of diarrhea do not require antibiotic therapy in healthy adults. However, in

Table 2. Clinical Features of Infectious Diarrhea

Feature	Location	
	Small bowel	**Large bowel**
Pathogens	*Salmonella*	*Campylobacter*
	Vibrio cholerae	*Salmonella*
	Escherichia coli (ETEC, EPEC)	*Shigella*
	Yersinia	*Yersinia*
	Rotavirus	*Escherichia coli* (EIEC, EHEC)
	Norwalk virus	*Clostridium difficile*
	Adenovirus	*Entamoeba histolytica*
	Giardia	Cytomegalovirus
	Cryptosporidium	
Location of pain	Mid abdomen or diffuse	Lower abdomen, rectum
Volume of stool	Large	Small
Type of stool	Watery	Mucoid, blood
Fecal leukocytes	Rare	Common
Other	Dehydration, malabsorption	Tenesmus if proctitis

EIEC, enteroinvasive serogroups; EHEC, enterohemorrhagic groups; EPEC, enteropathogenic strains; ETEC, enterotoxigenic strains.

Modified from Hamer DH, Gorbach SL. Infectious diarrhea and bacterial food poisoning. In: Feldman M, Sleisenger MH, Scharschmidt BF, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 2. 6th ed. Philadelphia: WB Saunders Company; 1998. p. 1594-632. Used with permission.

those presenting with bloody stools or high fever or those with a chronic illness, including immunocompromise, empiric antibiotic therapy is often provided while the results of stool culture are pending. Quinolones are usually given for empiric coverage in adults. The more common causes of bacterial diarrhea are summarized in Table 4.

Table 3. Summary of Viral Diarrhea

Virus	Incubation, days	Duration, days
Rotavirus	1-3	4-5
Norwalk virus	1-2	2-3
Adenovirus	8-10	7-14
Astrovirus	2-4	3-5

Modified 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.

Campylobacter

Campylobacter is the most commonly identified bacterial cause of diarrhea in the United States and is twice as common as *Salmonella* and sevenfold more common than *Shigella*. Most infections are due to *C. 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

Table 4. Summary of Bacterial Diarrhea

Bacteria	Incubation, days	Duration, days	Dysentery (blood/mucus)*	Source
Salmonella				Chicken, eggs, meat, dairy
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
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

**Scale: 0 = no to +++ = common.*
P-P, person-to-person.
Modified 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.

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, immunocompromise, 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 5). Infection can be complicated by bacteremia resulting in disseminated infection. *S. typhi* and *S. paratyphi* cause typhoid fever. The other serotypes (~2,000 described) cause nontyphoidal salmonellosis. *S. enteritidis* and *S. typhimurium* are the two 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*, in addition to eating raw or undercooked eggs and poultry, are listed in Table 6.

Gastroenteritis occurs in 75% of infections and typically begins within 48 hours after exposure, with nausea and vomiting, 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 7 or fewer 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,

Table 5. 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 >1 year	<1

AIDS, acquired immunodeficiency syndrome.
Modified from Hamer DH, Gorbach SL. Infectious diarrhea and bacterial food poisoning. In: Feldman M, Sleisenger MH, Scharschmidt BF, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 2. 6th ed. Philadelphia: WB Saunders Company; 1998. p. 1594-632. Used with permission.

Table 6. Conditions Predisposing to *Salmonella* Infection

Hemolytic anemia
Sickle cell disease
Malignancy
Lymphoma
Leukemia
Disseminated carcinoma
Immunosuppression
AIDS
Corticosteroids
Chemotherapy/radiation
Achlorhydria
Gastric surgery
Proton pump inhibitors
Idiopathic
Ulcerative colitis
Schistosomiasis

AIDS, acquired immunodeficiency syndrome.
Modified from Hamer DH, Gorbach SL. Infectious diarrhea and bacterial food poisoning. In: Feldman M, Sleisenger MH, Scharschmidt BF, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 2. 6th ed. Philadelphia: WB Saunders Company; 1998. p. 1594-632. Used with permission.

or osteomyelitis). Recurrent or persistent bacteremia can occur in patients with acquired immunodeficiency syndrome (AIDS).

Typhoid fever (enteric fever) is a systemic infection characterized by a longer 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 than diarrhea. Delayed bowel perforation and bleeding can occur. Physical findings include bradycardia related to fever, 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, 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, ~5 weeks), although most patients clear the organism within 3 months. Chronic carriage (>1 year) occurs in fewer 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 hydration 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 subjects with uncomplicated gastroenteritis. Antibiotics (eg, quinolones, amoxicillin, and trimethoprim-sulfamethoxazole [TMP-SMX]) are indicated for colitis, for patients with or at risk for

bacteremia (extremes of age, immunocompromise [HIV, medications, or malignancy], valvular heart disease, hemoglobinopathy, or orthopedic implants), for severe disease, or for chronic 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 empiric therapy while sensitivity data are pending. Resistance to chloramphenicol, TMP-SMX, and ampicillin makes these drugs inappropriate for empiric therapy. Corticosteroids also may be beneficial for patients with severe disease. In chronic 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 four species (*S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. 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. *S. 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 complaints 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*. *S. dysenteriae* 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 those with HLA-B27.

Treatment focuses on hydration and perhaps avoidance of antimotility agents. Healthy patients whose condition improves spontaneously may not require therapy. However, antibiotics have been shown to decrease the duration of disease and mortality. Therefore, for most patients, particularly those with chronic illnesses (including malnutrition and HIV), the elderly, day care or health care workers, or food handlers, antibiotic therapy (quinolones, TMP-SMX, or ampicillin) is indicated for 1 to 5 days, depending on the severity of the infection. Resistance to multiple antibiotics has been reported, and if therapy is begun before sensitivity data are available, quinolones are recommended (for adults). For all patients, handwashing and other hygienic practices are necessary to decrease person-to-person spread and to limit outbreaks.

Escherichia coli

Enterohemorrhagic *E. coli* (eg, *E. coli* O157:H7)

Enterohemorrhagic *E. coli* (EHEC) produces Shiga toxin and causes colitis after an incubation period of 3 to 5 days. *E. 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 of salami, sprouts, and unpasteurized milk or juice. Although the infectious dose is low, EHEC is effectively killed at temperatures higher than 156°F. 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 embraces irradiated foods remains to be seen.

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/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/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/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).

Patients with EHEC should be placed in contact isolation, and any personal contacts who have gastrointestinal 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 tetracycline) often are given empirically for moderate-to-severe traveler's diarrhea. As for most gastrointestinal infections, multiple-drug antibiotic resistance has been reported with ETEC, although resistance to quinolones does not appear to be a major problem yet.

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 1900s. 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. Antibiotics are effective therapy, 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. Resistance to TMP-SMX is common, but not to 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. Specific tests for EAEC are not available clinically. Quinolones are effective therapy, suggesting that empiric treatment with these agents may be reasonable for patients with HIV who have diarrhea and negative findings on evaluation.

The different types of *E. coli* are summarized in Table 7.

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.

V. 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 quinolones, doxycycline, or tetracycline.

V. 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 (up to 1 L/hour or more) 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 life-saving, but severe cases usually require intravenous fluids, with attention to potassium and bicarbonate replacement. Infection can be treated with various antibiotics, including tetracycline, doxycycline, TMP-SMX, or erythromycin, and even a single dose of quinolones can be effective.

V. vulnificus also can cause diarrhea. The organism can be acquired through wound contamination by infected 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 to 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

Table 7. Types of *Escherichia coli* Causing Infectious Diarrhea

Type	Patients affected	Pathophysiology	Clinical feature
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)	Rare, food and water outbreak	Direct invasion	Usually watery diarrhea, 10% have dysentery
Enterohemorrhagic (EHEC, eg, O157:H7)	Food (hamburger), sporadic or outbreak	Shiga-like cytotoxins	Watery then bloody diarrhea, HUS/TTP
Enteroaggregative (EAEC)	Infants in developing countries, HIV positive	Adherence, toxins	Prolonged watery diarrhea

HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.
Modified from Hamer DH, Gorbach SL. Infectious diarrhea and bacterial food poisoning. In: Feldman M, Sleisenger MH, Scharschmidt BF, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 2. 6th ed. Philadelphia: WB Saunders Company; 1998. p. 1594-632. Used with permission.

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 (cirrhosis, iron overload, or immunocompromise) 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 can simulate Crohn's 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, three or more separate stools should be analyzed.

Giardia lamblia

Giardia lamblia, 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 may present with 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 chronic 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. Metronidazole (250 mg 3 times daily for 5-7 days) is usually effective therapy. Treatment of asymptomatic carriers provides no benefit for the individual but may help prevent outbreaks, for example, in 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 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. Patients with severe colitis or abscesses may require intravenous therapy. 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.

Numerous nonpathologic amebae can inhabit the human colon, 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 polymerase chain reaction 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 10% to 50% 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 lamblia* or *Cyclospora cayetanensis*. The risk of infection can be decreased by avoiding uncooked foods, local water (including ice), and unpasteurized drinks.

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 with immunocompromise, severe chronic illness, hypochlorhydria, or 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. 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 4, are acquired from food and can be considered forms of "food poisoning." Also, some bacteria cause acute gastrointestinal symptoms from preformed toxins that are ingested with contaminated foods. Common symptoms of food poisoning and typical offending agents are listed in Table 8.

Staphylococcus aureus toxin causes 1 to 2 days of severe vomiting, cramps, and diarrhea that begin 2 to 6 hours after ingestion (eg, cream-filled pastries, meat, or potato or egg salad). Severe infection can cause dehydration.

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 (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 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.

Epidemiology

During the past 25 years, there has been an increase in the occurrence rate and a more modest clinical

Table 8. Food Poisoning Syndromes

Symptoms	Incubation period, hours	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), *V. parahaemolyticus*, *Yersinia*

EHEC, enterohemorrhagic Escherichia coli; *EIEC, enteroinvasive* E. coli; *ETEC, enterotoxigenic* E. coli.
Data from Guerrant RL, Bobak DA: Bacterial and protozoal gastroenteritis. N Engl J Med. 1991;325:327-40.

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.

C. difficile is detected in very few (1%-3%) healthy adults. It is more common in hospitalized adults and in patients receiving antibiotic therapy. 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*.

Populations at high risk for *C. difficile*-associated disease include the elderly; patients with uremia, burns, abdominal surgery, or cancer; and patients in an intensive care unit. It is not known whether these groups are more exposed to nosocomial infections or are more susceptible to *C. difficile*-associated disease because of their specific illnesses.

- Most cases of *C. difficile*-associated disease occur after antibiotic use, although other risk factors exist.
- *C. difficile*-associated disease ranges from asymptomatic carriage to diarrhea without colitis to colitis with or without pseudomembranes.
- *C. difficile* can be found in healthy infants but is uncommon in healthy adults.
- Most antibiotic-associated diarrhea is due to the antibiotic and not to *C. difficile*.
- Most pseudomembranous colitis is due to *C. difficile* infection.

Case Presentation

A 75-year-old man presented with 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 101°F, normal blood pressure, and a pulse rate of 98 beats/minute. The abdomen was mildly distended and tender without guarding or rebound. Laboratory studies showed leukocytosis of 13.4 cells × 10^9/L, 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 starting 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. Overall mortality rate is low (2%-3%), although it is higher among the elderly or debilitated patients (10%-20%) and with fulminant colitis or toxic megacolon (30%-80%). In some patients (5%-19%), disease is localized to the proximal colon and may manifest 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.

- *C. difficile*-associated disease usually occurs within 1 to 2 weeks after antibiotic therapy is started.
- In about 10% of patients, the disease is localized above the splenic flexure and the presentation can be atypical.

- From 10% to 25% of patients have recurrent disease.

Differential Diagnosis

Staphylococcal enterocolitis and typhlitis can occur in patients receiving chemotherapy and can have a presentation similar to that of *C. difficile*-associated disease. Exacerbation of Crohn's 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 (*Campylobacter*, *Salmonella*, *Shigella*, *E. coli*, *Entamoeba*, *Listeria*, 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, 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.

Diagnostic Testing

Diagnosis is based on a combination of clinical findings, laboratory test results, and sometimes 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 two or three 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) has excellent specificity and improved sensitivity compared with testing for either toxin alone, because some strains of *C. difficile* may produce only one toxin or the other.

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 cases, but colonoscopy may be required in about 10% of cases 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 (Fig. 1).

- *C. difficile*-associated disease is toxin mediated.
- Stool cytotoxicity assay is the standard diagnostic test, but it is expensive and time consuming.
- ELISA for toxin A or B is used in most laboratories because it is faster and less expensive than tissue culture. Its relatively poor sensitivity can be improved by testing two or three stool samples.
- For many patients, endoscopy is not necessary for diagnosis.

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, empiric 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 250 to 750 mg 3 or 4 times daily for 7 to 10 days. Because of concerns about cost and resistance with vancomycin, metronidazole is the preferred first-line therapy. However, metronidazole has more side 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 treatment for severely ill patients. Because oral vancomycin is poorly absorbed, a high stool concentration can be achieved without systemic side effects. The usual dose is 125 mg every 6 hours for 7 to 14 days. 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 side effect. Because cholestyramine binds vancomycin, they should not be given simultaneously.

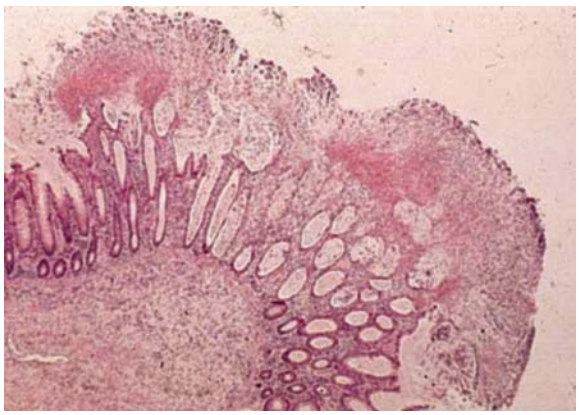

Fig. 1. Typical histologic appearance of pseudomembranous colitis.

Treatment of Recurrent Infection

Recurrent disease usually responds well to retreatment 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, for example, 125 mg 4 times daily for 4 to 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. A similar prolonged, tapering course of metronidazole can be considered, although side effects may increase with longer treatment. Another option is to give antibiotic and anion exchange resin for 5- to 7-day periods, alternating with periods when antibiotic treatment is withheld. Also, treatment with a combination of vancomycin and rifampin has been successful. Other regimens aim to suppress *C. difficile* with the use of oral *Lactobacillus* GG or nonpathogenic yeast (*Saccharomyces boulardii*) or with enemas containing feces from healthy subjects. However, none of these agents has been proved superior to standard therapy.

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

C. difficile spores 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, including 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.

- Metronidazole and vancomycin are equally effective, particularly for mild-to-moderate disease.
- If oral therapy is not possible, intravenous metronidazole may be useful. Intravenous vancomycin is not useful.
- Cholestyramine works by binding toxins, but it can bind vancomycin.
- Multiple recurrences of disease may require prolonged tapering or pulses of antibiotics, with or without additional therapy.

Summary

C. 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 index of suspicion 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. 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 represents cause and effect 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 fecolith, peritoneal contamination by feces may not occur. Stage IV indicates fecal peritonitis.

- Colonic diverticula are common but do not cause symptoms unless they are infected or bleeding.
- Diverticula form predominantly in the sigmoid colon by mucosal protrusion through weak spots in the bowel wall.
- Virtually all patients with diverticulitis have a microperforation.
- Stage I, small confined abscess; stage II, large confined abscess; stage III, suppurative peritonitis; stage IV, fecal peritonitis.

Clinical Features

Symptoms of diverticulitis include lower abdominal pain, fever, and altered bowel habits (typically diarrhea). The stool may contain trace blood, but profuse bleeding is very uncommon. Dysuria,

urinary frequency, and urgency reflect bladder irritation, whereas pneumaturia, fecaluria, or recurrent urinary tract infection suggests 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 the 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 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.

- A contrast enema shows diverticula but not inflammation.
- Indications for computed tomography: uncertain diagnosis or concern about an abscess.
- Sigmoidoscopy is necessary only to exclude carcinoma or colitis.

Treatment

Treatment is influenced by severity, ability to tolerate oral intake, previous history of diverticulitis or bleeding, and complications.

- *Mild first attack, tolerate oral intake*: 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% to 10% of patients will have a second attack within 2 years.
- *Severe pain, inability to tolerate oral intake, persistent symptoms despite adequate outpatient therapy*: Hospitalization, nothing by mouth, and broad-spectrum intravenous antibiotics. Computed tomography to exclude abscess or perforation. Consider computed tomography-guided percutaneous drainage of an abscess to control systemic sepsis, permitting a single-stage surgical procedure, if necessary, at a later stage.
- *Surgery*: Emergency operation is indicated for peritonitis, uncontrolled sepsis, perforation, and clinical deterioration. Indications for elective surgery include fistula formation, stricture, and recurrent diverticulitis.

If surgical treatment can be deferred until acute inflammation heals, then 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 two-stage procedure involves resection of the diseased segment and creation of an end colostomy with oversewing of the distal colonic or rectal stump (Hartmann's procedure). Colonic continuity may be reestablished in a second operation.

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CHAPTER 18

Colorectal Neoplasms

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Colorectal cancer is primarily a disease of urban, industrialized societies. In the United States, the lifetime risk for the development of this cancer is approximately 6%. Recent data have suggested that the incidence rates for 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 of proximal neoplasms (cecum to splenic flexure) include ill-defined abdominal pain, weight loss, and occult bleeding. The presentation of distal neoplasms (descending colon to rectum) may be 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 time of the initial diagnosis of colorectal cancer, 39% of patients have localized disease, 36% have regional metastases,

Abbreviations: AFAP, attenuated familial adenomatous polyposis; COX, cyclooxygenase; CT, computed tomography; FAP, familial adenomatous polyposis; MAP, MutYH-associated polyposis; SEER, Surveillance Epidemiology and End Results.

and 19% have distant metastases. Distant metastases typically occur in the liver, peritoneal cavity, and lung. Less common sites of metastases are the adrenal glands, ovaries, and bone. 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→mucosa at risk→adenoma→adenocarcinoma. Indirect evidence to support this adenoma-carcinoma 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 (Fig. 1). The *APC* tumor suppressor gene is considered the "gatekeeper" and is mutated in approximately 85% of all colorectal cancers. K-*ras* is the most frequently activated oncogene in colorectal neoplasms and is mutated in approximately 50% of large (≥1 cm) adenomas and adenocarcinomas. The *p53* gene appears to be mutated later in carcinogenesis, because chromosomal loss is relatively more common in malignant (70%-80%) than in benign neoplasms. DNA mismatch repair genes, including *MSH2*, *MLH1*, *PMS1*, *PMS2*, and *MSH6*, maintain nucleic acid sequence integrity during replication and have been termed *caretaker genes*. Mutations in these genes are found in 10% to 15% of sporadic colorectal cancers and are associated with microsatellite instability.

Polyp Subtypes

Adenomatous polyps are considered to have malignant potential, whereas hyperplastic,

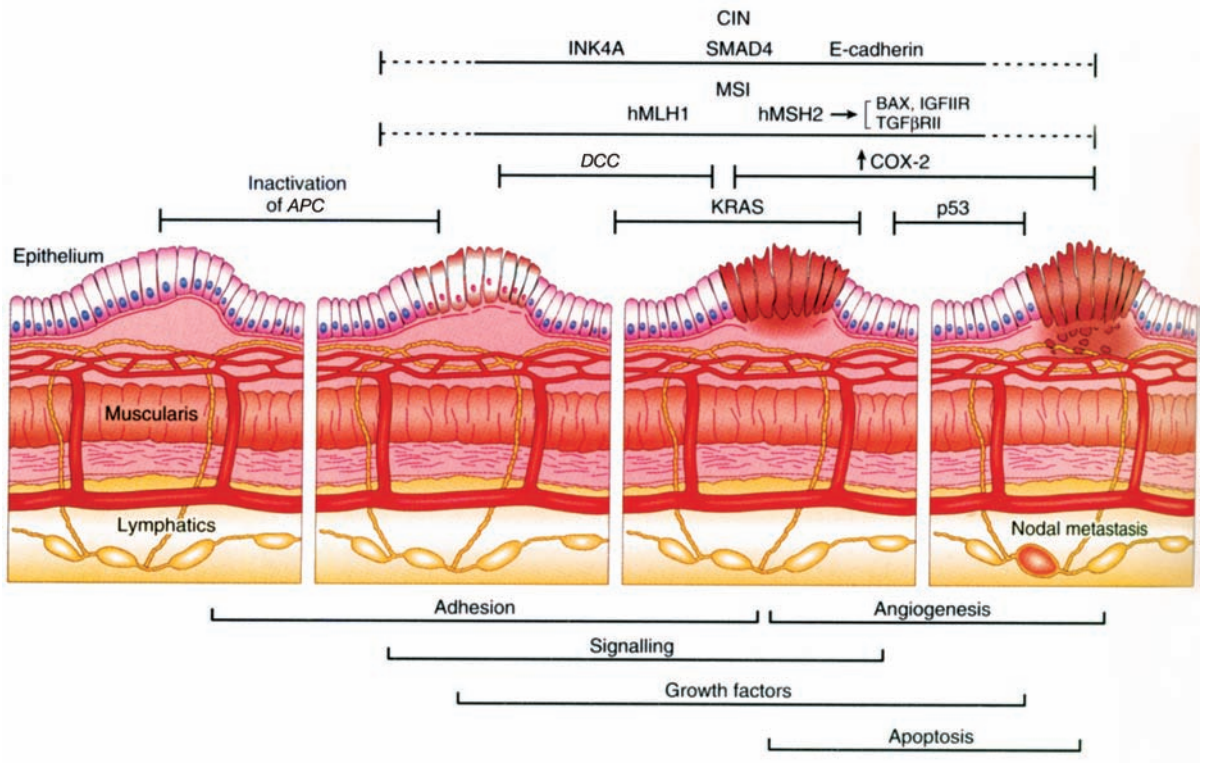

Fig. 1. Adenoma-to-carcinoma sequence and the associated molecular alterations involved in colon cancer development. *APC*, adenomatous polyposis coli; CIN, chromosomal instability; COX-2, cyclooxygenase-2; *DCC*, deleted in colorectal cancer; MSI, microsatellite instability. (From Niederhuber JE, Cole CE, Grochow L, Jacoby RF, Lee FT Jr, Mooney M, et al. Colon Cancer. In: Abbeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. Clinical oncology. 3rd ed. Philadelphia (PA): Elsevier; 2004. p. 1877-1941. Used with permission.)

inflammatory, and hamartomatous (juvenile) polyps generally do not. Serrated polyps also appear to confer at least some increased risk for future colorectal cancer, although the natural history of these neoplasms has not been characterized fully. 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 (three or more) 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 1). For colon cancers, the preoperative stage typically is determined by physical examination, computed tomography (CT), and chest radiography. For rectal cancer, endoscopic ultrasonography can provide additional information about the depth of tumor invasion and regional lymph node status. Final colorectal cancer stage incorporates pathology review of the resected tumor tissue. Pathologic stage 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%; IIa, 85%; IIb, 72%; IIIa, 83%; IIIb, 64%; IIIc, 44%; and IV, 8%. Five-year survival rates for rectal cancer are generally similar.

Table 1. Colorectal Cancer Staging

Stage	TNM classification
I	T1 or T2 N0 M0
IIa	T3 N0 M0
IIb	T4 N0 M0
IIIa	T1 or T2 N1 M0
IIIb	T3 or T4 N1 M0
IIIc	Any T N2 M0
IV	Any T any N M1
Overall	Any T any N any M

T category (primary tumor): T1, tumor invades through the muscularis mucosa and into the submucosa; T2, tumor invades through the submucosa and into the muscularis propria; T3, tumor invades through the muscularis propria and into the subserosa; T4, tumor invades through the entire colorectal wall and into nearby tissues or organs.

N category (regional lymph nodes): N0, no regional lymph node metastasis; N1, metastasis to 1-3 regional lymph nodes; N2, metastasis to ≥4 regional lymph nodes.

M category (distant metastasis): M0, distant metastasis is absent; M1, distant metastasis is present.

Modified from AJCC cancer staging manual. 6th ed. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al, editors. New York: Springer-Verlag; 2002. p. 116. Used with permission.

EPIDEMIOLOGY

General Distribution

Worldwide, colorectal cancer ranks fourth in cancer incidence for men and third for women. However, the incidence rates vary by global region (25-fold difference or more). Areas with the highest reported incidence rates for colorectal cancer include North America, Australia/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 for women are 44.6/100,000 and 16.4/100,000, respectively, and for men, the rates are higher at 60.8/100,000 and 23.5/100,000. From 1998 to 2004, the annual percentage change in colorectal cancer incidence rates was –2.5%; from 2002 to 2004, the annual percentage change in colorectal cancer mortality rates was –4.7%.

Race and Ethnicity

Of the five 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, and the 5-year survival rate is also less than that of Caucasian Americans. Although this likely is explained, at least in part, 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 relative to that in the distal colon and rectum.

HOST AND ENVIRONMENTAL FACTORS

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 for 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 subjects 60 years or older than among younger subjects.

Personal History of Colorectal Neoplasia

Persons with a personal history of colorectal adenomas or adenocarcinomas are at increased risk (up to sixfold) for additional, or metachronous, neoplasms. Adenoma characteristics associated with future tumor development include large size (>1 cm), villous histology, and three or more lifetime colonic adenomas. Neither hyperplastic polyps nor small, solitary tubular adenomas are strong risk factors for metachronous neoplasms. After resection of colorectal cancer, the annual incidence rate for 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 one first-degree relative with colorectal neoplasia diagnosed before age 60 years, or two or more first-degree relatives with colorectal neoplasia diagnosed at any age) appears to confer approximately a 1.5- to 2-fold increase in the risk of colorectal cancer.

Inflammatory Bowel Disease

Chronic ulcerative colitis is associated with a substantially increased risk of colorectal cancer over time. Cumulative incidence rates range from 2% after 10 years to 18% after 30 years of disease. The extent of colitis has been positively associated with colorectal cancer risk (pancolitis > distal colitis > proctitis), but the effects of disease activity have not been defined completely. Primary sclerosing cholangitis and a family history of colorectal cancer represent additional risk factors. However, the effects of disease activity on the risk of colorectal cancer are not conclusively known. Fewer data are available about the association between Crohn's disease and colorectal cancer, but the risk appears to be comparable to that of chronic ulcerative colitis among patients with inflammatory bowel disease of similar duration. Current data do not support an increased risk of colorectal cancer for patients with lymphocytic or collagenous colitis. Studies have suggested that inflammatory bowel disease-related tumors may develop through a different molecular pathway than sporadic neoplasia, with aneuploidy occurring early in the carcinogenic process.

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 one or several independent or codependent mechanisms. Generally, vegetable consumption has been one 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 by increased dietary fiber, subsequent intervention trials have not observed appreciable reductions in the risk of colorectal cancer.

Calcium binds to intraluminal toxins and also influences mucosal proliferation within the colorectum. In one clinical trial, calcium supplementation was associated with a statistically significant 19% decrease in the recurrence of adenoma in post-polypectomy 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, 1 mg/day of folic acid was found to be associated with increased risks for recurrent advanced adenomas as well as noncolorectal cancers.

Lifestyle

Alcohol induces cellular proliferation, blocks methyl group donation, and inhibits DNA repair. Many observational studies have suggested a twofold to threefold 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 as-yet-undefined mechanisms.

Other

A recent meta-analysis of data from 15 observational studies found that 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) (autosomal dominant). As many as one in five cases may represent new-onset

spontaneous mutations. The estimated prevalence is 1/5,000 to 7,500 persons. Additional genetic and environmental factors, as yet unidentified, 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, with typically hundreds to thousands of adenomas developing sometime during adolescence. Other findings include duodenal adenomas, gastric (fundic) gland hyperplasia, mandibular osteomas, and supernumerary teeth. In the absence of prophylactic colectomy, colorectal carcinoma is inevitably diagnosed in patients with FAP at a mean age of approximately 40 years. Even after colectomy, increased cancer risks remain, particularly in the periampullary region of the duodenum and in the retained rectal remnant (if partial colectomy was performed).

Gardner's syndrome is a variant of FAP in which patients with *APC* mutations have the same phenotypic features as classic FAP but in addition 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

Attenuated FAP (AFAP) is associated with relatively fewer adenomas (<100) and later onset of colorectal cancer (approximate age, 55 years) than in classic FAP. About 40% of these cases can be found to be 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 flexible sigmoidoscopy, as recommended for screening in classic FAP kindreds.

Lynch Syndrome

Lynch syndrome (formerly 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 (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 called the Amsterdam criteria (Table 2). The syndrome has been associated recently with mutations in at least five DNA mismatch repair genes. 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. Jarvinen et al. reported that regularly performed colonoscopy with polypectomy can decrease the risk of large-bowel adenocarcinoma for persons with Lynch syndrome by approximately 60%.

Turcot's Syndrome

Turcot's syndrome refers to a familial predisposition for both colonic polyposis and central nervous system tumors. It likely represents 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 (FAP variant), whereas those with DNA mismatch repair gene mutations are prone to the development of glioblastoma multiforme (Lynch syndrome variant). Of interest, glioblastoma multiforme that arises in the setting of Turcot's syndrome tends to occur at an earlier age and has 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.

Table 2. Clinical Criteria for Diagnosing Lynch Syndrome

≥3 Relatives with Lynch syndrome-related cancers*
≥1 Persons with colorectal cancer is a first-degree relative of 2 other cases
≥2 Successive generations affected
≥1 Persons with colorectal cancer diagnosed before age 50 years

**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 of AFAP, but patients with MAP who have more than 100 adenomas have been described. 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 for 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 cancers (duodenum, jejunum, ileum, pancreas, biliary tree, and gallbladder), ovarian sex cord tumors, Sertoli cell testicular tumors, and breast cancer.

Tuberous Sclerosis

Tuberous sclerosis (autosomal dominant) 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. Both *PTEN* and *SMAD4* mutations 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, fewer than five 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 refers to a noninherited condition manifested by signs and symptoms of malnutrition or malabsorption. Gastrointestinal hamartomas may be present and can exhibit foci of adenomatous epithelium. 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.

PREVENTION

Screening and Surveillance

For average-risk patients (defined as asymptomatic adults, 50 years or older, without other known risk

factors for colorectal cancer), several screening options have been endorsed by major primary care and subspecialty organizations, as follows:

- Fecal occult blood test or fecal immunochemical test every year
- Flexible sigmoidoscopy every 5 years
- Fecal occult blood test or fecal immunochemical test every year plus flexible sigmoidoscopy every 5 years
- Double-contrast barium enema every 5 years
- Colonoscopy every 10 years

Also, emerging technologies, such as CT colonography and DNA-based stool tests, show considerable promise. 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 or 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 one first-degree relative diagnosed at age 60 years or older, or two 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 to 10 years after the onset of pancolitis. Patients with proctosigmoiditis and no other identifiable risk factors for colorectal cancer can be managed with annual colonoscopy with surveillance biopsies 12 to 15 years after the onset of distal colitis

History of Colorectal Neoplasia

After a complete clearing colonoscopy has been performed, repeat examinations can be delayed for patients who have one or two 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 post-polypectomy 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 two or three therapeutic colonoscopies should prompt a surgical consultation. 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 refers to 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 anti-inflammatory drugs are structurally diverse, yet 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 regular use of nonsteroidal antiinflammatory drugs and colorectal tumors. The chemopreventive effects of these drugs are thought to be derived through cyclooxygenase (COX)-2 inhibition, and agents that selectively block this enzyme isoform (celecoxib and rofecoxib) have been shown in several large clinical trials 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

Colon Cancer

In the absence of known distant metastases or prohibitive comorbid conditions, surgical excision is the initial treatment modality for most patients who have colon cancer. 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 such as subtotal colectomy or proctocolectomy can be performed for patients who have colorectal neoplasia in multiple colonic segments or familial cancer syndromes, respectively. Operative intervention also may be considered for selected patients who have isolated liver or lung metastases. Postoperative, or adjuvant, 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 includes 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) 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 as T3 and higher or N1 and higher with CT and endoscopic ultrasonography. Adjuvant chemotherapy with 5-fluorouracil and leucovorin (with or without oxaliplatin) is recommended for patients with stage II or stage III rectal cancer. Molecularly targeted therapies (eg, bevacizumab and cetuximab) are being investigated as adjuvant therapy and have demonstrated clear benefits for patients with metastatic colorectal cancer.

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CHAPTER 19

Irritable Bowel Syndrome

G. Richard Locke III, MD

Irritable bowel syndrome (IBS) is a common condition that contributes substantially to health care costs. Historically, because the cause is not known and no curative therapy is available, IBS has been managed symptomatically. 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 therapy directed at behavioral intervention has been used more extensively than in the past. The overall goal is to improve the patient's symptoms and overall quality of life and, ideally, to prevent the suffering that patients experience.

DEFINITION

The symptom criteria for IBS are listed in Table 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 et al in 1978. However, a goal of the Rome criteria 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

Table 1. Diagnostic Criteria for Irritable Bowel Syndrome*

Recurrent abdominal pain or discomfort† at least 3 days per month in the last 3 months associated with *2 or more* 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

**Criteria fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.*

†Discomfort means an uncomfortable sensation not described as pain.

From Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006;130:1480-91. Used with permission.

Abbreviation: IBS, irritable bowel syndrome.

helpful. The more criteria a specific patient meets, the more likely the patient is to have IBS. Nonetheless, the diagnosis can be made only if there are not any structural or metabolic abnormalities that explain the symptoms.

EPIDEMIOLOGY

IBS is thought to be a common condition. Many population-based surveys have assessed the individual symptoms of this syndrome. The prevalence rates for symptom reporting have varied between 8 and 22 per 100 adults. It is simplest to think of the prevalence of IBS as 10% (1 in 10).

Although many studies have assessed the prevalence of IBS, data on incidence are more difficult to obtain. Because not everyone with the syndrome seeks medical care, data on incidence need to come from a population-based study. The exact numbers have varied among surveys, but over a 1-year period about 10% of the general population report the onset of symptoms of IBS. 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. A recent 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 seeking of health care by persons with the syndrome. 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 female-to-male ratio in the community is approximately 2:1. Thus, sex may have a role not only in the onset of the syndrome but also in health care-seeking behavior. The prevalence of IBS decreases slightly with age. However, the new onset of symptoms may occur in the elderly. Prevalence estimates now are available from around the world. 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 among patients with IBS who are 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. However, other studies have shown that seeking health care for gastrointestinal problems is increased among children of parents with gastrointestinal symptoms. Additional study is needed to separate nature from nurture in the development of IBS.

Symptoms of IBS can occur after acute inflammatory conditions such as *Salmonella* infection. The propensity for development of postinfectious IBS is associated with sex, duration of illness, and the psychologic state of the person at the time of infection. Inflammatory markers have been identified in the colons of people with postinfectious IBS. The concept of postinfectious IBS is being actively investigated.

Food allergies or sensitivities also may have a role in the development of IBS. Patients with symptoms of this syndrome report more sensitivity to food than people without symptoms. However, the data on exclusion diets have not shown convincingly that food is a cause of the symptoms. Recently, a trial of dietary modification based on IgG antibodies to food antigens did show an effect.

PATHOGENESIS

The cause of IBS is not understood completely. However, IBS has been associated consistently with visceral hypersensitivity. Balloon distention studies have shown that patients with this syndrome feel discomfort at a lower volume than do subjects without the syndrome. Patients with IBS and subjects without IBS do equally well on tests of somatic pain such as cold water immersion, suggesting that IBS is a disorder specific to the gut. Balloon distention studies also have suggested that patients with IBS have hypersensitivity throughout the gastrointestinal tract. The frequent

overlap between IBS and fibromyalgia and urinary symptoms suggests that the problem may be an even more diffuse visceral hypersensitivity.

More recently, imaging studies of the central nervous system during balloon distention have shown that a different part of the brain is activated during balloon distention in patients with IBS than in healthy controls. Considerable advances have been made in understanding this brain-gut axis. The concept of a "big brain" in the cranial vault and a "little brain" in the abdomen has gained widespread acceptance. With this understanding, research has been undertaken to evaluate compounds that have central nervous system activity to determine whether they have a role in the management of IBS. Serotonin has been investigated most intensively. The pathophysiologic state of carcinoid diarrhea shows that serotonin has a role in gastrointestinal physiology. Other studies have shown that serotonin has a role in visceral hypersensitivity, which increasingly is viewed as the primary pathophysiologic mechanism of IBS. The roles of opioid receptors, cholecystokinin receptors, dopamine receptors, cannabinoid receptors, and α-adrenergic agonists are being actively investigated.

Increasing attention is now focused on the role of the bacteria in the gastrointestinal tract and the development of symptoms of IBS. Bacterial overgrowth may be the cause of IBS in such patients. Whether this is true or the bacterial overgrowth is the result of an underlying dysmotility is being studied.

DIAGNOSIS

IBS is diagnosed on the basis of symptom criteria (Table 1), in the absence of structural or metabolic 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, and giardiasis are all relatively common conditions that can have similar symptoms. Carcinoid syndrome, microscopic colitis, bacterial overgrowth, and eosinophilic gastroenteritis also can have similar symptoms, but they are less common. The problem is that IBS is so common that it is difficult to justify performing extensive diagnostic tests on a large proportion of the population. All tests will 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 (Fig. 1). Patients older than 50 years need a full colonic evaluation to exclude colorectal cancer.

Recent studies have heightened the awareness about celiac disease. Although much needs to be learned about how common the diagnosis of this disease is among patients who present with symptoms of IBS, clinicians should consider some form of testing for the disease in these patients.

As noted, bacterial overgrowth has been reported in patients with IBS. The proportions have varied greatly (10%-70%), which may reflect the validity of the tests used. Whether people with bacterial overgrowth should still be considered to have IBS or given a separate diagnosis is an open question.

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 the 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 symptoms 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 (Fig. 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 high fiber diet may be helpful for patients who alternate between constipation and diarrhea, but the benefit of a high fiber diet

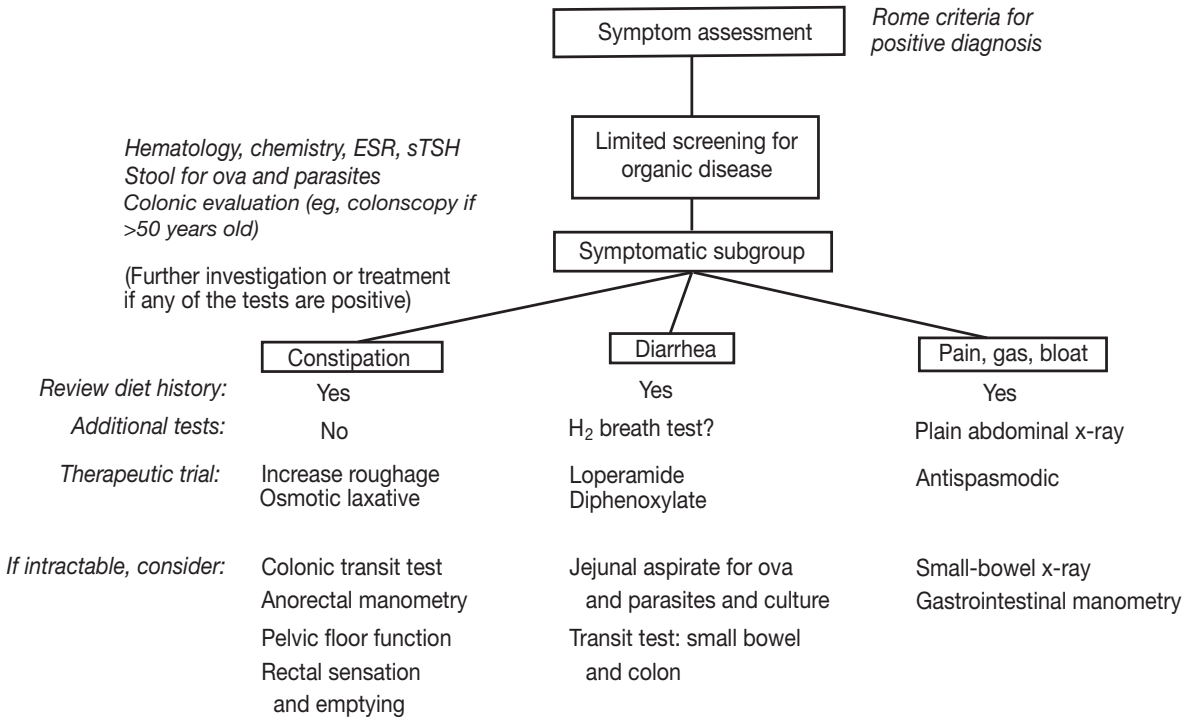

Fig. 1. Management of irritable bowel syndrome. *ESR*, erythrocyte sedimentation rate; *sTSH*, sensitive thyroid-stimulating hormone. (Modified from Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. Gastroenterology. 1997;112:2120-37. Used with permission.)

in diarrhea-predominant IBS is unproven. Antispasmodic agents are appropriate for patients who have primarily abdominal pain. These agents have been prescribed because of the belief that the pathophysiologic mechanism of IBS is spasms and irregular 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.

For patients with diarrhea, stool chemistry tests for surreptitious laxative abuse, duodenal aspirate for bacterial overgrowth, colonic biopsies for microscopic colitis, determination of urinary 5-hydroxyindoleacetic acid for carcinoid syndrome, and a small-bowel colonic transit study may all be considered. 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, alosetron, or even octreotide may be considered.

Many physicians consider pain-predominant IBS the most challenging to manage. 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.

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 or selective serotonin reuptake inhibitors has provided improvement for many patients. The pathophysiologic mechanism of tricyclic antidepressants is not clear. The dosages used are much lower than those used to treat depression. In a randomized clinical trial, tricyclic antidepressants were helpful for people who did not experience side effects (per protocol analysis). In the intention-to-treat analysis, cognitive behavioral therapy was shown to be effective. Patients with IBS refractory to other treatment may benefit from formal pain management approaches.

HEALTH CARE UTILIZATION

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 one study, subjects with IBS in the community were found to incur an extra $300 annually in health care expenditures. Extrapolated to the US population, this 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

During the past few years, important changes have occurred in the management of IBS. The traditional approach of reassurance and a high fiber diet is no longer adequate for everyone. Symptomatic care likely will remain the appropriate treatment for patients with mild symptoms. However, for patients with pronounced gastrointestinal symptoms, more aggressive approaches will be necessary. In time, the role of newer medications will be established. Similarly, the adjunctive use of behavioral intervention will gain wider use.

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CHAPTER 20

Constipation and Disorders of Pelvic Floor Function

Adil E. Bharucha, MBBS, MD

CONSTIPATION

Colonic Motor Physiology and Pathophysiology: Salient Aspects

Function

Colonic functions include the 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 800 to 1,000 mEq of sodium and chloride daily. In healthy subjects, 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 in the section on "Disorders of Pelvic Floor Function.")

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 quiescence (particularly at night) to isolated contractions, bursts of contractions, or propagated contractions. In contrast to the small intestine, rhythmic migrating motor complexes do not occur. 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

Abbreviations: 5-HT, 5-hydroxytryptamine; MR, magnetic resonance; MRI, magnetic resonance imaging; PNTML, pudendal nerve terminal motor latency.

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 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's 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 explaining their 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 and relaxation distal to the distended segment. 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 or small intestinal (or both) transit 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 seven 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 effects of 5-HT are as follows:

Motor—Stimulation of serotoninergic 5-HT_4 receptors facilitates both components of the peristaltic reflex, that is, 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, for example, nitric oxide or vasoactive intestinal polypeptide, which relax smooth muscle.

Sensory—5-HT_3 and 5-HT_4 receptors are located on intrinsic primary afferent neurons, which initiate peristaltic and secretory reflexes. 5-HT_3 receptors also are located on extrinsic sensory afferents and vagal afferents, partly explaining why 5-HT_3 antagonists reduce nausea.

Other—Central 5-HT participates in the regulation of appetite, sexual function, and mood.

Assessment of Colonic Transit

Colonic transit can be measured with commercially available radiopaque markers (Sitz 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 eight or more markers seen on plain films on day 3 or by five or more markers seen on day 5. With scintigraphy, the isotope (generally 99m Tc or 111In) 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 and the rectum; counts in these areas are weighted by factors 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 (Fig. 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 radiopaque markers are comparable to those made with scintigraphy. The radiopqaue 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 present for at least 3 months, with a total symptom duration of 6 months or longer. *Functional constipation* is defined by two or more of the following symptoms: 1) fewer than three defecations per week, 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 two of the following three 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 (Tables 1 and 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, that is, hard small pebbles or watery stools, characterized by the Bristol stool form scale, correlate strongly with delayed and accelerated colonic transit, respectively. In contrast to stool frequency recorded by diaries, frequency based on recall alone does not correlate with colonic transit. Certain symptoms (prolonged

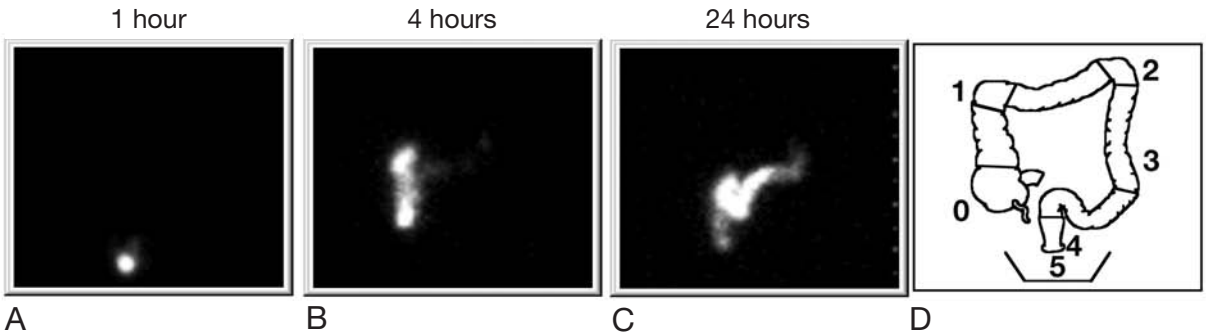

Fig. 1. Scintigraphic assessment of colonic transit. Note isotope progression through, *A*, cecum (1 hour), *B*, ascending colon (4 hours), and, *C*, transverse colon (24 hours). *D*, Numbers represent average isotope distribution corresponding to a geometric center of 1 to 5. In this patient, the geometric center at 24 hours was 1.7 (normal, 1.7-4.0). (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: Elsevier; 2005. p. 279-98. Used with permission.)

Table 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's disease, spinal cord disease, autonomic neuropathy, multiple sclerosis
Psychologic—anorexia nervosa

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.

Practical Classification of Constipation

After secondary causes of constipation are excluded, colonic transit and anorectal functions should be assessed in patients with constipation that does not respond to dietary fiber supplementation (Table 3). This approach facilitates the management of chronic constipation. *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 may also have abdominal pain, but by definition the pain is not relieved by defecation or associated temporally with harder or less frequent stools. Pelvic floor function should be assessed in refractory constipation because symptoms alone cannot distinguish among constipation resulting from pelvic floor dysfunction, normal transit, and slow transit. Most patients with obstructive defecation 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.

Table 2. Common Medications That Cause Constipation

Analgesics—opiates, nonsteroidal antiinflammatory drugs
Antihypertensives—calcium channel blockers, α_2-agonists, diuretics (↓ potassium)
Antacids containing aluminum, calcium
Anticholinergics, antidepressants, antihistaminics, antiparkinsonian agents
Long-term laxative use
Others—iron, cholestyramine

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 intake can cause or exacerbate constipation, whereas refeeding may restore colonic transit.

Medical Therapy

Dietary fiber supplementation either in foods or as 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 tsp up to 3 times daily; Konsyl, 2 tsp twice daily; calcium polycarbophil (FiberCon), 2 to 4 tablets daily; bran, 1 cup daily. Fiber supplements are more effective in normal-transit or "fiber-deficiency" constipation than in slow-transit constipation or pelvic floor dysfunction. Fiber supplementation should start at a small dose administered twice daily (AM and PM) with fluids or meals, increasing the dose 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 over days, as with a laxative. Bloating may be

Table 3. Classification of Functional Constipation

Feature	Normal	Delayed	Normal/delayed
Pelvic floor function	Normal	Normal	Abnormal
Category	Normal-transit	Slow-transit	Obstructive defecation
Management	Fiber supplementation	Fiber supplementation Laxatives Surgery	Biofeedback therapy

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 to 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 to 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 subjects. Both agents may cause transient abdominal cramps and flatulence. They are equally effective for treating constipation in the elderly. However, lactulose ($1.32-$2.65 per dose) is extremely sweet and more expensive than sorbitol ($0.14-$0.27 per dose). 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, rarely progressing to chronic renal impairment and long-term dialysis, has been reported in 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 (greater severity for patients 57 years and 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).

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 can cause acute phosphate nephropathy and renal failure.

Stimulant laxatives affect mucosal transport and motility and 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 cohorts and a recent case-control study failed to find 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.

Tegaserod maleate is a partial 5-HT_4 receptor agonist that accelerates small-bowel transit and tends to accelerate colonic transit in patients with constipation-predominant irritable bowel syndrome. Tegaserod was approved for treating constipation-predominant irritable bowel syndrome in women and chronic constipation in patients younger than 65 years. In clinical trials of constipation-predominant irritable bowel syndrome, data from weekly self-administered questionnaires indicated response rates of 46% for tegaserod and 34% for placebo. For chronic constipation, the primary end point was an increase in one complete (feeling of complete evacuation), spontaneous (not preceded by laxative use within 24 hours) bowel movement per week during the first 4 weeks compared with baseline. For this end point, the response rates at 4 and 12 weeks were 25% and 28% for placebo, respectively, 39% and 38% for tegaserod 2 mg twice daily, and 43% and 45% for tegaserod 6 mg twice daily. Differences between tegaserod 6 mg twice daily and placebo were significant at 4 and 12 weeks; for tegaserod 2 mg twice daily, differences were significant at 4 weeks only. Subgroup analyses did not show significant therapeutic benefit for patients older than 65 years. The main side effect was diarrhea (6.6% for tegaserod 6 mg twice daily compared with 3% for placebo); tegaserod was not associated with a higher incidence of abdominal surgery or ischemic colitis than placebo. In 2007, tegaserod was withdrawn from the market because a review of the clinical trial data showed a higher incidence (P=.024) of cardiovascular ischemic events (myocardial infarction, unstable angina pectoris, and stroke) in patients who received tegaserod than in those who received placebo (13 per 11,614 patients [0.11%] vs. 1 per 7,031 patients [0.01%], respectively). All patients who had cardiovascular ischemic events had preexisting cardiovascular disease or cardiovascular risk factors.

Lubiprostone is a novel bicyclic fatty acid derivative that promotes intestinal secretion by activating intestinal chloride channels. Lubiprostone accelerates colonic transit in healthy subjects, and studies, which have been published mainly in abstract form only, suggest that it improves symptoms in chronic constipation. The only phase II study published in full suggested that lubiprostone improved stool consistency and frequency and self-reported severity of constipation. However, effects on abdominal bloating, discomfort, and straining were less impressive. Lubiprostone is well tolerated; nausea and headache are the most common side effects. In clinical trials, 33% of patients reported nausea, which generally was mild and could be reduced by taking medication with meals.

- Lubiprostone stimulates intestinal secretion by activating chloride channels; it also improves stool consistency and relieves constipation.

Other pharmacologic approaches that have been used to manage constipation include colchicine and misoprostol (Cytotec). Colchicine, 0.6 mg orally 3 times daily, and misoprostol, 1,200 μg daily, cause diarrhea. Colchicine should be used cautiously, if at all, for treating constipation, because long-term use may be associated with neuromyopathy. Other side 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 who do not have a response 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%. The prevalence of functional defecatory disorders in the community is unknown. 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 (Fig. 2). 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 (Fig. 3). 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

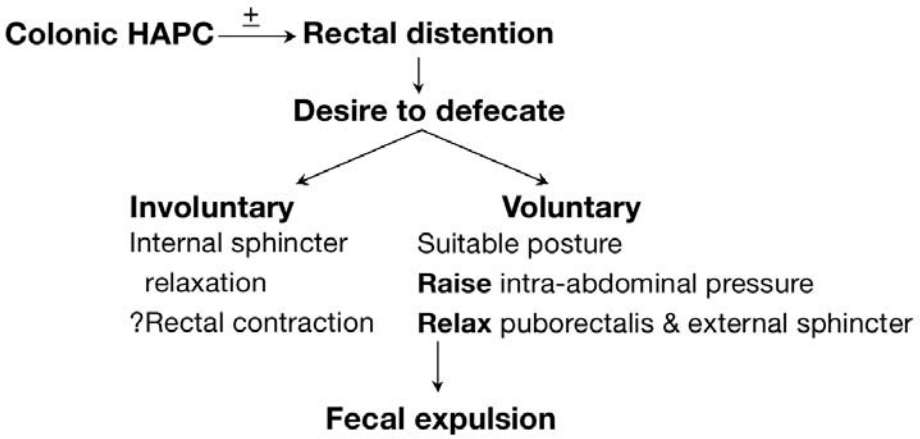

Fig. 2. Physiology of defecation. HAPC, high-amplitude propagated contraction. (From Bharucha AE, Camilleri M. Physiology of the colon. In: Zuidema GD, Yeo CJ, editors. Shackelford's surgery of the alimentary tract. Vol IV. 5th ed. Philadelphia: WB Saunders Company; 2002. p. 29-39. Used with permission.)

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 some combination of these. Although certain symptoms are considered suggestive of obstructive defecation (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 subjects 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

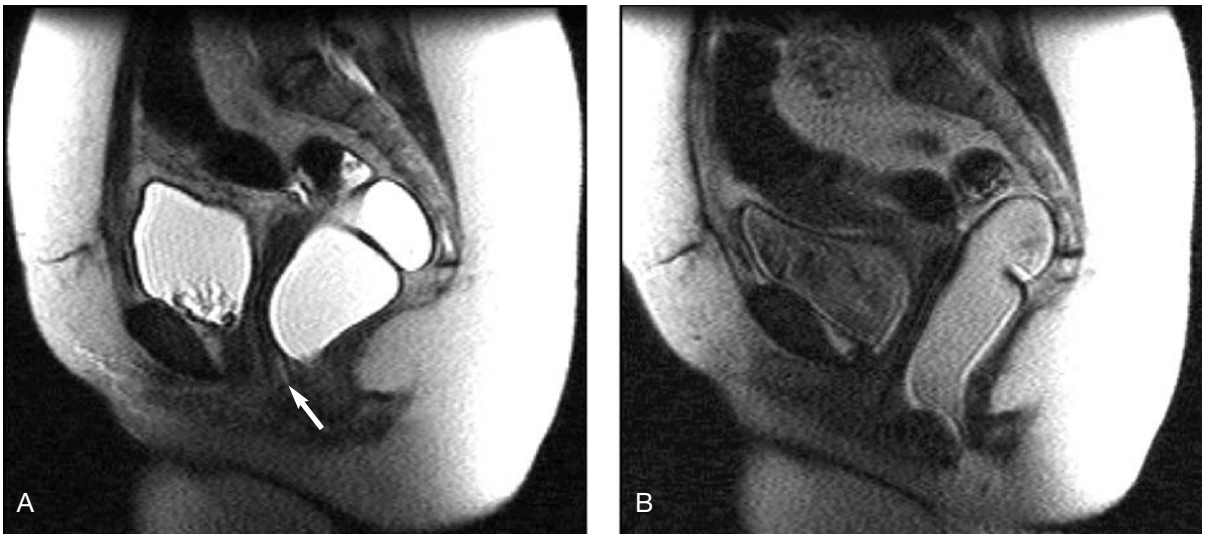

Fig. 3. Magnetic resonance fluoroscopic images of the pelvis at rest (*A*) and during simulated defecation (*B*). Defecation is accompanied by opening of the anorectal junction (*arrow*), pelvic descent, and widening of the anorectal angle from 101° at rest to 124° during defecation. The rectum was filled with ultrasound gel.

and puborectalis muscles contract; the latter 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 increased resting pressure and/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—This test may indicate a high resting anal sphincter pressure (>90 mm Hg) or a reduced rectoanal pressure gradient (or both) during simulated defecation (Fig. 4). Normal values for anal pressures measured with manometry are technique-dependent and influenced by age, sex, and perhaps parity. Anal pressures are lower in women than in men and decrease with age, even in asymptomatic subjects.

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, subjects with normal pelvic floor functions can expel a rectal balloon within 3 to 5 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 (Fig. 5). 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 (MR) proctography—During dynamic (ie, barium or MR) proctography, anorectal anatomy and pelvic floor motion are recorded with the patient at rest, 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 is easier to visualize the bladder and uterus together with the anorectum, and 3) the bony landmarks (pubis and sacrococcygeal junction) necessary to measure anorectal descent are visualized more distinctly during MRI. Therefore, measurements of anorectal motion are more reproducible with MR proctography than 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 the primary abnormality.

Colonic transit—Up to 70% of patients with pelvic floor dysfunction have delayed colonic transit. Thus, the finding of slow colonic transit does not exclude the diagnosis of obstructive defecation.

- 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

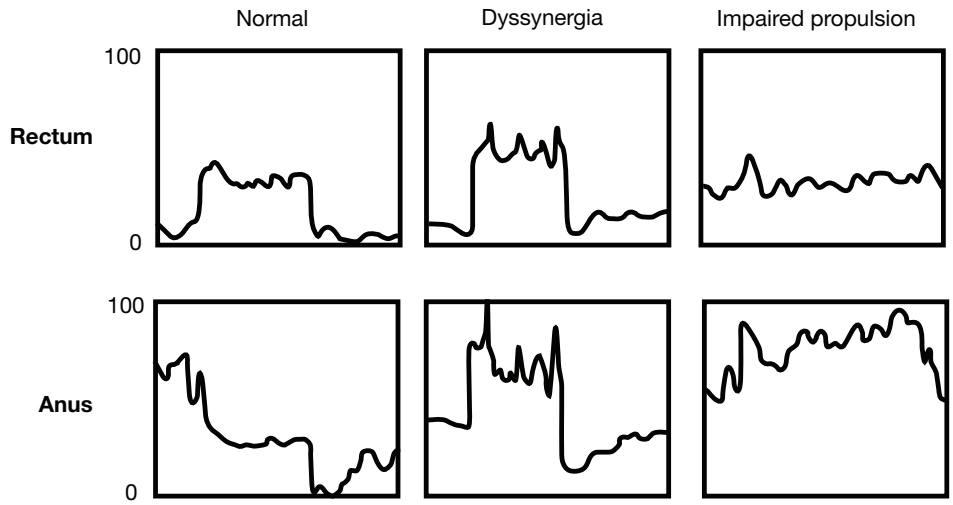

Fig. 4. Rectoanal pressure profiles during defecation in health and functional defecatory disorders (dyssynergia and impaired propulsion). In contrast to the normal pattern (*left*) (ie, increased rectal pressure and anal relaxation) during simulated evacuation, patients with defecatory disorders may either paradoxically contract the anal sphincters (*center*) or generate inadequate rectal propulsive forces (*right*).

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 abdominal wall and diaphragmatic contraction and pelvic relaxation during defecation. Measures to contract the pelvic floor muscle (eg, Kegel's exercises) are not appropriate for obstructive defecation. Strong rapport between patients and therapists is critical for biofeedback therapy. 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 1 in 10 of all women and 1 in 5 women 40 years and 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

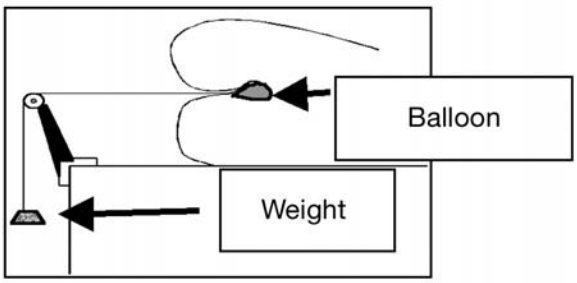

Fig. 5. Balloon expulsion test. (From Bharucha AE, Klingele CJ. Autonomic and somatic systems to the anorectum and pelvic floor. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Vol 1. 4th ed. Philadelphia: Elsevier; 2005. p. 279-98. Used with permission.)

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 the 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. Important diseases that contribute to fecal incontinence include the following:

Sphincter damage—This 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—This 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—These include multiple sclerosis, Parkinson's disease, Alzheimer's 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 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 time, 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, both with the patient in the left lateral decubitus position and 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 (Fig. 6).

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 subjects. 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—This reliably identifies anatomical defects or thinning of the internal anal sphincter and defects of the external anal sphincter that often are unrecognized clinically or 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 up to one-third of women develop an external anal sphincter defect 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 there is a high index of suspicion for excessive perineal descent, a significant rectocele (eg, in patients who 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 subjects to report when they perceive the first detectable sensation, the desire to defecate (or urgency), and maximal tolerable discomfort during rectal balloon distention, generally with a handheld syringe. Alternatively, a

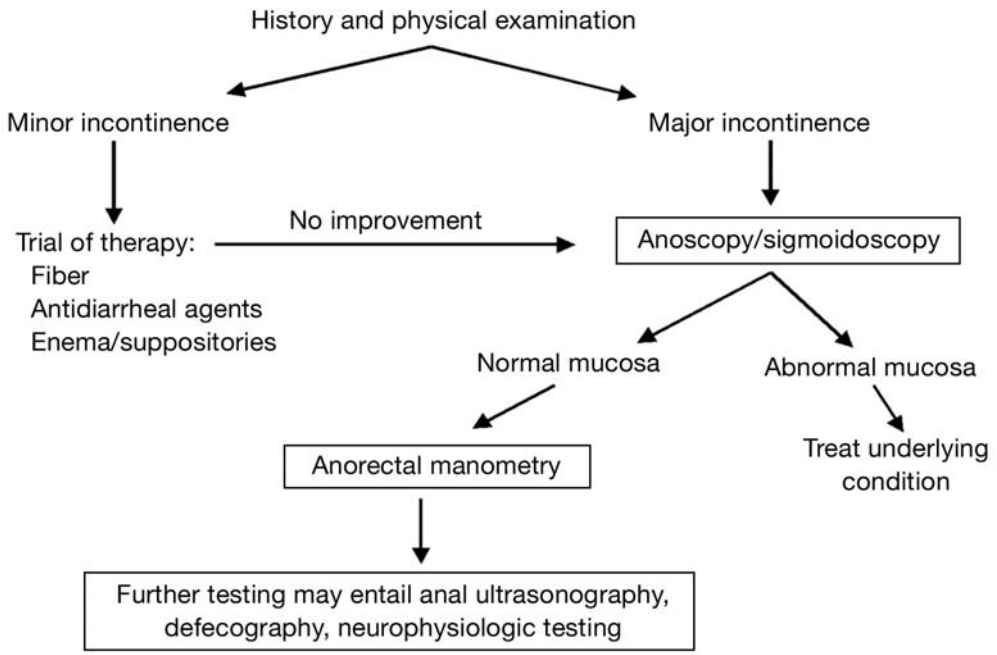

Fig. 6. Algorithmic approach to fecal incontinence.

balloon can be inflated at a controlled rate by 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 (4 mg; maximal dose, 16 mg/day), 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 resin cholestyramine is useful for patients with post cholecystectomy 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 four groups: standard medical and nursing care (advice only), advice and verbal instruction on sphincter exercises, hospital-based computer-assisted sphincter pressure biofeedback, or hospital biofeedback and use of a home electromyographic biofeedback device. Overall, 75% 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 four 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, published in abstract form only. Thirty-six percent of 168 patients with fecal incontinence responded (21%) or withdrew (14%) after medications, education, and behavioral strategies for 4 weeks. Of the other 108 patients, adequate relief was reported by 77% of those assigned randomly to electromyographic-assisted biofeedback therapy but by only 41% of those assigned randomly to Kegel's exercises alone. 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. Artificial anal sphincter and dynamic graciloplasty are associated with considerable morbidity, particularly wound infections, and are used

sparingly in the United States. Colostomy is often the last resort for patients with medically refractory fecal incontinence. Several uncontrolled studies have suggested that sacral nerve stimulation may improve fecal continence, particularly in patients who have normal sphincter anatomy. Sacral nerve stimulation is approved for treating urinary symptoms but, pending completion of a controlled trial, not for fecal incontinence.

- Conservative measures, including management of bowel disturbances, often can 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.

Colon

Questions and Answers

QUESTIONS

Abbreviations used:
ALT, alanine aminotransferase
AST, aspartate aminotransferase
BUN, blood urea nitrogen
CT, computed tomography
ECG, electrocardiography
ED, emergency department
EGD, esophagogastroduodenoscopy
ELISA, enzyme-linked immunosorbent assay
NSAID, nonsteroidal antiinflammatory drug

Multiple Choice (choose the best answer)

1. 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 blood. He reports no significant abdominal pain and has not had fever. He has not taken antibiotics in recent weeks and does not have a recent travel history. On examination, the patient is afebrile, has mild nonspecific abdominal tenderness, and active bowel sounds. Laboratory studies show no evidence of leukocytosis, and stool testing shows the presence of many fecal leukocytes. What would you do next?

a. Request stool culture and, on the basis of the result, decide on the necessity of antibiotics
b. Initiate empiric antibiotic therapy while awaiting stool culture
c. Initiate empiric antibiotic therapy without performing stool culture
d. Perform flexible sigmoidoscopy
e. Colonoscopy

2. While making rounds on the hospital service, your resident presents a 65-year-old man who was admitted through the ED with 5 days of diarrhea, which has been bloody for the last 2 days. He has remained hemodynamically stable overnight with intravenous hydration and is afebrile. Overnight, his diarrhea is no better. The laboratory results are as follows:

	Yesterday AM in ED	This AM
Leukocytes, $\times 10^9$/L	18	19.5
Hemoglobin, g/dL	12.9	10.2
Platelets, $\times 10^9$/L	198	110
Na^+, mEq/L	143	139
K^+, mEq/L	4.0	3.6
Creatine, mg/dL	1.1	1.5
BUN, md/dL	31	45
AST, U/L	44	110
ALT, U/L	32	31

Which of the following organisms is most likely?

a. *Yersinia*
b. Toxigenic *Escherichia coli*
c. Norwalk-like virus (Norovirus)

d. *Clostridium difficile*
e. *Escherichia coli* O157:H7

3. A 24-year-old man comes to the ED with watery diarrhea. His gastrointestinal symptoms had begun 48 hours earlier with nausea and vomiting. After the patient had eaten at a Chinese restaurant, he developed nausea and vomiting, which lasted for 12 hours, and then developed watery diarrhea. He has not had fever, recent antibiotics, or infectious contacts. He has not taken any new medications and has no significant medical history. On clinical examination, he is afebrile and has moist mucous membranes. Abdominal examination discloses hyperactive bowel sounds but is otherwise unremarkable. The most likely cause of the patient's acute diarrhea is:

a. *Staphylococcus aureus*
b. *Bacillus cereus*
c. *Clostridium perfringens*
d. *Listeria monocytogenes*
e. *Clostridium difficile*

4. A 74-year-old woman presents with a 2-week history of watery diarrhea. The patient reports passing 6 to 8 watery stools daily. She has not had any bloody stools. She has had nocturnal diarrhea. There has been associated nausea without vomiting. She has not reported fever. The patient has a history of diabetes mellitus (type 2), and treatment was switched recently from metformin to insulin. 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 abdominal examination shows mild nonspecific tenderness. Stool studies show the presence of many leukocytes. A stool sample is negative for *Clostridium difficile* toxin by ELISA. What would you do next?

a. Initiate treatment with loperamide and titrate to symptom control
b. Prescribe prednisone 40 mg daily
c. Prescribe metronidazole 500 mg 3 times daily for 10 days
d. Prescribe vancomycin 125 mg 4 times daily for 10 days
e. Send two additional stool samples for *Clostridium difficile* toxin testing

5. An 80-year-old man is evaluated for bloody diarrhea, which has been present for 5 days. The patient states that initially he experienced vague abdominal discomfort associated with low-grade fever and he felt he may have had a virus. Next, watery diarrhea developed, which initially seemed to improve but subsequently became bloody diarrhea and has been present for 5 days. He thinks that he may have had low-grade fever intermittently over the past 72 hours, but this has not been documented. He has had no recent antibiotic therapy. The patient has been looking after his 4-year-old grandson, who attends a local daycare facility and has had a recent febrile illness with diarrhea. On clinical examination, the patient's vital signs are normal but mucous membranes are dry. Stool testing shows multiple leukocytes. The most likely cause of this man's illness is:

a. *Salmonella typhi*
b. *Clostridium difficile*
c. Enteroinvasive *Escherichia coli*
d. *Shigella*
e. *Giardia lamblia*

6. Choose the most accurate statement:

a. Environmental factors contribute to about 40% of all cases of colorectal cancer
b. Calcium supplementation likely increases the risk of colorectal cancer
c. Body mass index is inversely associated with the risk of colorectal cancer
d. Colorectal cancer can be considered a tobacco-related disease

7. Choose the most accurate statement:

a. Existing data indicate that regular screening has a beneficial effect on fatal, but not incident, colorectal cancer
b. More than one-half of US adults older than

50 years are in adherence with the screening recommendations for colorectal cancer
c. Digital fecal occult blood testing should be performed as part of an annual physical examination
d. Screening colonoscopy has been shown in three randomized, controlled trials to reduce colorectal cancer risk

8. Which of the following is not an endorsed option for average-risk colorectal cancer screening?

a. Fecal occult blood test or fecal immunochemical test every year
b. Flexible sigmoidoscopy every 5 years
c. Double-contrast barium enema every 5 years
d. Flexible sigmoidoscopy + double-contrast barium enema every 5 years
e. Colonoscopy every 10 years

9. Choose the most accurate statement about malignant polyps:

a. Surgical resection should be pursued in all cases
b. Surgical resection should be pursued if dysplastic cells have spread through the muscularis mucosae
c. Surgical resection should be pursued if dysplastic cells have invaded the polyp stalk
d. Endoscopic resection is adequate for some cases

10. A 52-year-old woman has a brother who died of colon cancer (microsatellite instability-high phenotype) at age 40 years. Her brother underwent gene testing, and a germline mutation was detected in *MLH1*. The patient has a *negative* gene test (no mutation found). What screening does she need?

a. Colonoscopy every 6 months
b. Colonoscopy annually
c. Colonoscopy every 3 years
d. Colonoscopy now and every ten years

11. A 69-year-old woman presents with a 5-month history of watery diarrhea. She has not had any recent change in her diet, has not traveled, and has not taken any new medications, including antibiotics. She has mild abdominal pain and five bowel movements daily but no weight loss, fevers, or gastrointestinal tract bleeding. The physical examination findings are unremarkable, and the results of blood tests are normal. Colonoscopic findings were normal, but mucosal biopsy specimens showed collagenous colitis. The diarrhea has not responded to loperamide up to 16 mg/day or mesalamine 4.8 g/day, each given for a 6-week period. What is the appropriate next step?

a. High-dose loperamide (up to 32 mg/day)
b. Bismuth subsalicylate (9 tablets/day)
c. Sulfasalazine (4 g/day)
d. Prednisone (40 mg/day)

12. A 36-year-old man has had ulcerative colitis for 16 years. It is in remission with a regimen of mesalamine 4.8 g/day. On the last surveillance colonoscopy, the mucosa showed only changes of quiescent colitis. Three biopsy specimens from the descending colon show low-grade dysplasia, which is confirmed by a second gastrointestinal pathologist. What is the appropriate next step?

a. Add azathioprine 2 mg/kg daily
b. Prescribe an NSAID for chemoprevention
c. Follow-up colonoscopy with intensive repeat biopsies in 6 to 12 months
d. Referral to surgeon for left hemicolectomy
e. Referral to surgeon for total proctocolectomy

13. A 21-year-old woman with terminal ileal Crohn's disease has abdominal pain and diarrhea that are refractory to trials of mesalamine, budesonide, and azathioprine. There is no fever and no evidence on CT for abscess or obstruction. She then is treated with infliximab, 5 mg/kg. Shortly after the infusion of infliximab is initiated, flushing, headache, nausea, chest heaviness, and mild dyspnea develop. Vital sign changes are also noted (blood pressure of 118/76 mm Hg and pulse of 66 at baseline and 101/60 and 88, respectively, currently), but findings on examination of the

heart and lungs are normal, as are ECG findings. What would be the appropriate next step in her management?

a. Reassure her that this is a common infusion reaction and continue infusion
b. Stop the infusion, and monitor symptoms. If they resolve, restart infusion at the standard rate
c. Stop the infusion, administer acetaminophen and diphenhydramine. Administer bolus of 500 mL of normal saline. If symptoms resolve, restart infusion at a lower rate
d. Stop the infusion and admit the patient for treatment and observation
e. Stop the infusion. The patient is allergic to infliximab; it cannot be used again

14. A 45-year-old man with an 8-year history of ulcerative colitis with multiple exacerbations began his current flare 3 weeks ago while receiving treatment with mesalamine, 4.8 g/day. After 5 days of treatment with prednisone, 40 mg/day, failed, he was admitted to the hospital and treated with methylprednisolone, 60 mg/day intravenously. His vital signs and abdominal examination findings remain stable. However, he has not had a response to 5 days of intravenous therapy. His past medical history is significant for chronic renal insufficiency attributed to chronic hypertension, which is poorly controlled, with blood pressure averaging 168/98 mm Hg. The patient has no prescription insurance and has difficulty paying for his medications. Laboratory results included the following: hemoglobin 10.2 g/dL, leukocytes 13.1×10^9/L (neutrophils 75%), creatinine 2.9 mg/dL, potassium 3.2 mEq/L, magnesium 1.2 mg/dL, cholesterol 105 mg/dL, and albumin 3.4 g/dL. What would you recommend at this point?

a. Increase the dose of methylprednisolone to 100 mg/day
b. Intravenous cyclosporine beginning at a dose of 4 mg/kg daily
c. Intravenous infliximab at a dose of 5 mg/kg
d. Surgical consultation for proctocolectomy with ileal pouch anal anastomosis

15. A 55-year-old man with a 15-year history of ulcerative pancolitis was found to have dysplasia, and he underwent proctocolectomy with mucosectomy of all rectal mucosal tissue and the creation of a hand-sewn ileal pouch anal anastomosis. His baseline bowel function postoperatively was four to six loose bowel movements per day without any urgency, bleeding, or abdominal pain. Two years postoperatively, he developed diarrhea with 8 to 10 watery bowel movements per day that are associated with mild rectal bleeding, cramps, and urgency. Endoscopy of his pouch showed inflammation and superficial ulceration throughout the pouch. The ileum above the pouch appeared normal. Biopsy specimens from the pouch showed mild to moderate acute inflammation without granulomas or crypt abscesses. What is the most likely explanation for this exacerbation?

a. Crohn's disease
b. Ulcerative colitis in residual rectal tissue
c. Ischemia of the pouch
d. Lymphoma of the pouch
e. Acute pouchitis

16. A 46-year-old woman is referred by her primary care physician for further management of collagenous colitis. She presented with chronic nonbloody diarrhea associated with a 30-lb weight loss. Flexible sigmoidoscopy and barium enema findings were normal, but colon biopsy specimens showed collagenous colitis. Treatment with loperamide and cholestyramine were without benefit. After telephone consultation with you, the primary care physician prescribed bismuth subsalicylate, 3 tablets 3 times daily, and mesalamine, 1,600 mg 3 times daily, each for 8 weeks. Neither of these drugs had any significant effect in controlling the patient's diarrhea, and the patient is referred to you. The next appropriate step in this patient's management would be:

a. Prednisone, 60 mg/day
b. Increase bismuth subsalicylate to 6 tablets 3 times daily
c. Determine the antiendomysial antibody level

d. Budesonide, 9 mg/day
e. Colonoscopy

17. A 25-year-old woman has a 4-week history of rectal pain and tenesmus. Three or four bowel movements per day are of normal consistency but usually are blood streaked. Also, she intermittently passes blood without a bowel movement. She states that she does not have any notable abdominal pain, nausea, vomiting, or weight loss. Initial laboratory studies are unremarkable except for hemoglobin of 10.2 mg/dL. Physical examination findings are normal other than blood on the examining finger on rectal examination. Colonoscopy shows normal mucosa in the distal ileum and throughout the colon down to the sigmoid colon. The rectum and sigmoid colon have active colitis with diffuse inflammation and mucosal ulceration. Biopsy findings are consistent with ulcerative colitis. Which of the following would be the most appropriate therapy?

a. Mesalamine suppositories
b. Hydrocortisone enema
c. Mesalamine enema
d. Oral mesalamine (Pentasa)
e. Oral budesonide

18. A 22-year-old woman presents with a 3-month history of increasing right lower quadrant abdominal pain and nonbloody diarrhea. She has lost 10 lb and recently had two episodes of increased mid abdominal pain, distention, vomiting, and decreased stool output that resolved after 1 or 2 days. She has had two urinary tract infections, and a recent urine culture grew *Klebsiella*, *Escherichia coli*, and yeast. She has not noticed pneumaturia, fecaluria, vaginal symptoms, fevers, chills, or sweats. She is a smoker and has a family history of Crohn's disease (an aunt and a cousin). On physical examination, she is thin and pale but in no acute distress. Tender fullness is noted in the right lower quadrant without guarding or rebound. Colonoscopic findings were negative, although the endoscopist was not able to intubate the terminal ileum. Which of the following tests would be most appropriate for establishing the diagnosis?

a. Small-bowel follow-through
b. Enteroclysis
c. Small-bowel capsule enteroscopy
d. CT enterography
e. EGD

19. A 38-year-old man with ulcerative colitis has been receiving maintenance therapy with mesalamine 4.8 g/day. Although compliant with this therapy, he developed a severe flare. His symptoms did not respond to prednisone, and he was hospitalized and treated with intravenous methylprednisolone. Stool studies at admission showed no infection. After 5 days of intravenous corticosteroid therapy, his symptoms are resolving and treatment is switched to oral prednisone. In addition to tapering prednisone, which of the following would be most appropriate for maintenance therapy in this patient?

a. Maintain on mesalamine
b. Maintain on lowest possible dose of prednisone
c. Initiate azathioprine therapy
d. Initiate cyclosporine therapy
e. Initiate methotrexate therapy

20. A 37-year-old woman with distal ileal Crohn's disease has been receiving maintenance therapy with mesalamine. For 2 weeks, she has had increasingly severe right lower quadrant abdominal pain, with six to eight bowel movements per day, nausea, anorexia, and a 10-lb weight loss. She states that she has no bleeding, vomiting, abdominal distention, or fever. On physical examination, she appears mildly acutely ill but without abnormal vital signs. The abdomen is mildly tender in the right lower quadrant, without mass, guarding, or rebound tenderness. CT enterography shows inflammation in the distal 15 cm of the ileum but no abscess. Colonoscopy shows fissuring ulcers in the distal ileum, with no evidence of colitis. Which of the following would be most appropriate for acute management of this flare?

a. Balsalazide
b. Prednisone

c. Metronidazole
d. Budesonide
e. 6-Mercaptopurine

21. A 31-year-old man with ileal Crohn's disease has been receiving maintenance therapy with mesalamine (Pentasa), 4 g/day. Four weeks ago, he developed increasing right lower quadrant abdominal pain with nonbloody diarrhea and anorexia. He was treated empirically with prednisone, 40 mg/day by mouth. Over the ensuing 2 weeks, he has had worsening of his symptoms, with low-grade fever but no gastrointestinal tract bleeding. On physical examination, he appears acutely ill with pallor. His temperature is 38.0°C, with a pulse rate of 98 and blood pressure of 106/50 mm Hg. He has normal bowel sounds, with tender fullness in the right lower abdomen but without guarding or rebound tenderness. The leukocyte count is 15.5×10^9/L, with a predominance of neutrophils. Treatment with broad-spectrum antibiotics is begun in the emergency department, and the patient is admitted to the hospital. Which of the following would be the most appropriate next step?

a. Flexible sigmoidoscopy
b. Colonoscopy
c. Abdominal CT scan
d. Cyclosporine
e. Infliximab

ANSWERS

1. Answer a
The patient has presented with an acute biphasic diarrheal illness: initially watery diarrhea, subsequently bloody diarrhea. Many fecal leukocytes were seen on stool analysis. Such a biphasic presentation may be seen with *E. coli* and *Shigella* infections. Most cases of *Campylobacter* infection do not require antibiotic therapy, but *Shigella* infection should be treated with antibiotics (highly infectious). Therefore, the optimal strategy is to await stool culture before making a decision about the necessity of antibiotics. Flexible sigmoidoscopy and colonoscopy are not indicated, given the acute presentation. Were the patient elderly, and at risk for ischemic colitis, endoscopic assessment may be reasonable.

2. Answer e
The constellation of symptoms and laboratory findings is most suggestive of hemolytic uremic syndrome complicating an infection with *E. coli* O157:H7. This occurs more often in the elderly or very young, and the risk may be increased with the administration of antibiotic therapy. *Shigella* is also an invasive pathogen and can cause bloody diarrhea, but it is not associated with hemolytic uremic syndrome. The other infections listed typically result in watery diarrhea.

3. Answer b
If nausea and vomiting are the predominant initial symptoms in a case of suspected food poisoning, the most likely cause is *Staphylococcus aureus*, *Bacillus cereus*, or *Clostridium perfringens*. In this particular case, the ingestion of Chinese food makes *Bacillus cereus* the most likely cause of the patient's symptoms. *Listeria monocytogenes* may cause an acute gastroenteritis after the ingestion of foods such as soft cheese and lunch meats. *Listeria* is of particular concern in the case of an immunocompromised host or a pregnant woman. *Clostridium difficile* is unlikely without previous use of antibiotics.

4. Answer e
The patient has significant watery diarrhea, including nocturnal diarrhea and fecal leukocytes. With the history of antibiotic use, *Clostridium difficile*-related diarrhea is most likely. The sensitivity of a single negative ELISA-based *C. difficile* stool toxin test is approximately 70%. The sensitivity of combining three ELISA-based *C. difficile* stool toxin tests is approximately 95%. Therefore, when *C. difficile* is suspected, up to three sequential stool samples should be sent for analysis, to confirm the correct diagnosis, before therapy is initiated.

5. Answer d
Salmonella and *Giardia* infection typically present with nonbloody diarrhea. *Shigella*, Enterohemorrhagic *Escherichia coli*, and Enteroinvasive *E. coli* may all cause bloody diarrhea. However, the biphasic

nature of the patient's presentation, with watery diarrhea initially, followed by bloody diarrhea, makes *Shigella* infection the most likely diagnosis. The fact that this patient was caring for a grandchild attending daycare also makes the diagnosis of *Shigella* infection more likely.

6. Answer d
Colorectal cancer can be considered a tobacco-related disease.

7. Answer b
More than one-half of US adults older than 50 years are in adherence with the screening recommendations for colorectal cancer.

8. Answer d
Flexible sigmoidoscopy + double-contrast barium enema every 5 years.

9. Answer d
Endoscopic resection is adequate for some cases.

10. Answer d
Colonoscopy now and every 10 years.

11. Answer b
Uncontrolled case series have suggested that mesalamine is effective in only a small proportion of patients with microscopic colitis, and sulfasalazine appears to be no more effective. The diarrhea did not improve with 16 mg of loperamide per day, and there is no reason to expect that increasing the dose would be of any benefit. Bismuth subsalicylate (Pepto-Bismol) is one of the few therapies shown in a controlled trial to be effective in microscopic colitis, with 60% to 70% of patients having improvement after 8 weeks. Although budesonide is not an option, it is the best studied medication in treating collagenous colitis and is highly effective. However, many patients have relapse after budesonide therapy is stopped; therefore, Pepto-Bismol should be tried before budesonide, especially in a patient with mild symptoms, as in this case. Prednisone is also very effective. However, the risk of recurrence is high after discontinuation of treatment, and the side effects of prednisone are likely to be more significant than those of bismuth or budesonide.

12. Answer e
Low-grade dysplasia in the context of chronic ulcerative colitis carries a high-risk of coexisting cancer (10%-20%) or progression to high-grade dysplasia or cancer (50%) within the next 5 years. Therefore, many authorities recommend total proctocolectomy for a patient with low-grade dysplasia. Because the patient is currently asymptomatic and biopsy specimens did not show active inflammation, adding immunosuppressive therapy is not indicated. Although NSAIDs likely have a chemopreventive effect, there is no evidence that they can prevent progression after dysplasia is present. Furthermore, long-term use of NSAIDs may increase the risk of a colitis flare. Partial resection is almost never performed in patients with ulcerative colitis and dysplasia. Although there may be less morbidity related to hemicolectomy, leaving in place portions of the colon with chronic colitis is thought to carry an unacceptably high risk of exacerbation or further development of dysplasia or carcinoma.

13. Answer c
Acute infusion reactions are relatively common with infliximab and are usually mild and resolve with discontinuation of the infusion and treatment with acetaminophen and antihistamines and, sometimes, corticosteroids. Intravenous fluids are administered if hypotension is present; epinephrine may be used for severe reactions. If symptoms respond and the reaction was mild, the infusion can be restarted, typically at a slower rate. Most mild infusion reactions do not require hospitalization. It would be inappropriate, however, to continue the infusion while the patient is having the reaction. If a patient has an infusion reaction, pretreatment with acetaminophen and antihistamines, with or without corticosteroids, is typically used for subsequent infusions.

14. Answer d
The patient has not had a response to an appropriate course of intravenous corticosteroids. There is no evidence that a higher dose would be more effective, and there is little evidence that prolonged treatment would increase his chance of having a response. Cyclosporine is effective for steroid-refractory ulcerative colitis. However, this patient has several contraindications to cyclosporine

therapy, including poorly controlled hypertension and chronic renal insufficiency. Also, hypocholesterolemia and hypomagnesemia both increase the risk of seizures from cyclosporine. Infliximab is also effective for ulcerative colitis that is refractory to steroid therapy, but this patient lacks prescription coverage and infliximab is expensive. Therefore, for this patient, surgery is the most appropriate next step. He is young and would be expected to do well with an ileal pouch anal anastomosis.

15. Answer e

The patient's symptoms are consistent with acute pouchitis or Crohn's disease of the pouch. Inflammation limited to the pouch is more consistent with pouchitis, and inflammation in the ileum above the pouch would suggest Crohn's disease. The histologic findings are classic for acute pouchitis. There is no evidence for granulomas, which would suggest Crohn's disease, and the histologic findings are not compatible with ischemia or lymphoma. Residual rectal tissue may be left behind after a total proctocolectomy with ileal pouch anal anastomosis (particularly with a stapled anastomosis, less so after mucosectomy, as was done in this case). Although this residual rectal mucosa can become inflamed because of recurrent ulcerative colitis (also called *cuffitis*), the amount of tissue should be small and easily distinguished from inflammation of the entire pouch, as in this patient.

16. Answer c

The appropriate treatment algorithm for microscopic colitis has not been established completely because of the lack of randomized controlled trials. Nonetheless, the patient has received appropriate treatment trials from her primary care physician. The next option to consider is corticosteroid therapy, preferably with budesonide rather than prednisone because of the fewer side effects. However, before corticosteroid therapy is initiated, it is appropriate to exclude celiac sprue, which is associated with collagenous colitis and may be responsible for lack of response of some patients to initial therapy. It is particularly important to exclude celiac sprue in the case of this patient who has had significant weight loss. If the patient does not have celiac sprue, budesonide therapy would be appropriate. If the patient does not have a response to corticosteroid therapy, ileostomy may be necessary to help control the diarrhea and improve the quality of life, but this is rarely needed in collagenous colitis. Colonoscopy would not be expected to add significantly to the information obtained recently with sigmoidoscopy and a barium enema study.

17. Answer c

With inflammation extending into the sigmoid colon, suppositories would not be sufficient treatment because they deliver the drug only to the rectum. For this patient's proctosigmoiditis, enemas are a good choice for therapy. Mesalamine enemas are superior to hydrocortisone enemas. Oral mesalamine would be an alternative if the patient did not tolerate or have a response to the enemas. However, the Pentasa formulation begins delivering active drug in the small intestine. For delivery to the left colon, a formulation that delivers drug more distally, such as Asacol, Lialda, or an azo-bond 5-acetylsalicylic acid product, would be more appropriate. Budesonide is absorbed in the distal ileum and proximal colon and would not be appropriate therapy for the patient.

18. Answer d

The patient's presentation suggests Crohn's disease with two recent episodes of partial small-bowel obstruction. The recurrent urinary tract infections and recent polymicrobial infection suggest an enterovesical fistula, and the tender right lower quadrant fullness suggests a possible abscess. With negative colonoscopic findings, the small intestine needs to be assessed. Because of the recent obstructive symptoms, capsule enteroscopy is contraindicated. Small-bowel follow-through and enteroclysis would be reasonable tests to evaluate the small intestine, but CT enterography provides the added benefit of looking at structures outside the bowel lumen and, in particular, can assess for a fistula or abscess. In the absence of significant upper gastrointestinal tract symptoms, EGD is not indicated at this time.

19. Answer c

A severe flare of ulcerative colitis developed in the patient while he was receiving full-dose mesalamine therapy. Therefore, attempting maintenance with

mesalamine would likely have a high risk of recurrent failure. Long-term corticosteroid therapy is neither effective nor safe for maintenance therapy. Similarly, long-term cyclosporine therapy has a high risk of toxicity without strong evidence of a maintenance benefit. Azathioprine and 6-mercaptopurine are widely used in this setting for maintenance therapy, with good evidence of benefit. There is no evidence of a maintenance effect with methotrexate in ulcerative colitis.

20. Answer d

The patient presents with a moderately severe flare of Crohn's disease while taking mesalamine. Evaluation shows disease limited to the ileum. In this setting, switching to a 5-aminosalicylate acid product that delivers drug to the colon (balsalazide) would not be appropriate. Antibiotics sometimes are used for mild to moderate Crohn's disease, but efficacy appears to be limited and, if seen, tends to be only in those with colonic or ileocolonic disease. 6-Mercaptopurine would be a reasonable medication for long-term maintenance therapy in this patient, but efficacy is delayed; therefore, this agent is not appropriate for acute management. In this setting, corticosteroid therapy often leads to prompt improvement. Prednisone is effective but has a risk of side effects. Budesonide is a potent corticosteroid designed to be most active in the terminal ileum, with less toxicity than prednisone. Therefore, it is the most appropriate treatment for the patient.

21. Answer c

This patient with a flare of ileal Crohn's disease has not had a response to oral prednisone. He has worsening symptoms and fever, with tender fullness in the right lower quadrant, which is worrisome for the development of an abscess. Therefore, before immunosuppressive therapy is initiated with cyclosporine or infliximab, CT should be performed. It is debated whether intravenous corticosteroid therapy should also be delayed until abscess is excluded by a CT study. In the acute setting, colonoscopy likely will not provide useful information, and flexible sigmoidoscopy would be even less helpful in this patient with ileal disease and no suggestion of rectal inflammation, such as hematochezia.

Section VI

Liver

CHAPTER 21

Approach to the Patient With Abnormal Liver Tests and Fulminant Liver Failure

John J. Poterucha, MD

Gastroenterologists should be able to evaluate liver test abnormalities in an efficient, cost-effective manner and to manage appropriately patients who have acute liver failure. To help gastroenterologists achieve these goals, this chapter includes the following:

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. Diagnostic algorithms for evaluating patients who have abnormal liver tests
6. Management of patients who have fulminant liver failure

COMMONLY USED LIVER TESTS

Aminotransferases (Alanine and Aspartate Aminotransferases)

The aminotransferases (also referred to as *transaminases*) are located in hepatocytes and, thus, are markers of liver cell injury (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 is relatively specific for liver injury, whereas AST is found not only in hepatocytes but also in skeletal and cardiac muscle and in other organs. ALT has a longer half-life than AST; thus, improvements in ALT levels lag behind those of AST. Marked muscle injury can produce striking increases in AST levels and, to a lesser extent, in ALT levels.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

Alkaline Phosphatase

Alkaline phosphatase is an enzyme located on the hepatocyte membrane bordering bile canaliculi (the smallest branches of the bile ducts). 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 if the increase is from liver or 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 the hepatocyte and conjugated with glucuronic acid to form monoglucuronides and diglucuronides. Conjugation makes bilirubin water-soluble, allowing it to be excreted in bile. 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 50% or more conjugated bilirubin. 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 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 produced 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 vitamin K improves prothrombin time within 2 days in a vitamin K-deficient patient but has no effect if the prolonged prothrombin time is due to liver disease with poor synthetic function.

Because albumin has a half-life of 21 days, decreases due to liver dysfunction do not occur acutely; however, the serum level of albumin can decrease relatively quickly in a patient who has a severe systemic 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.

HEPATOCELLULAR DISORDERS

Diseases that primarily affect hepatocytes are termed *hepatocellular disorders* and are characterized predominantly by increased levels of aminotransferases. The disorders are best categorized as *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 1.

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 the levels of aminotransferases, often more than 1,000 U/L. Generally, ALT increases more than AST. Aminotransferase levels 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

Table 1. 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 withdrawal of agent
Alcoholic hepatitis	History of alcohol excess AST:ALT >2 AST <400 U/L	Liver biopsy, improvement with abstinence
Ischemic hepatitis	History of severe hypotension	Rapid improvement of aminotransferase levels

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen.

most often in patients with preexisting cardiac dysfunction. Aminotransferase levels improve within a few days. Another cause of a transient increase in aminotransferase levels is transient obstruction of the bile duct, usually from a 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. Patients with alcoholic hepatitis frequently have an increase in bilirubin level out of proportion to the increase in aminotransferase levels.

Diseases producing sustained (>3 months) increases in aminotransferase levels are included in the category of chronic hepatitis. The increase in aminotransferase levels generally is more modest (2-5 times) than that in acute hepatitis. Although patients may be asymptomatic, they occasionally complain of fatigue and right upper quadrant pain. The most important and common disorders that cause chronic hepatitis are listed in Table 2.

Risk factors for hepatitis C include a history of blood transfusions or intravenous drug use. Patients with hepatitis B may be 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 or 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 higher levels of aminotransferases than do those with other disorders that cause chronic hepatitis. Autoantibodies, hypergammaglobulinemia, and other autoimmune disorders are helpful clues to the diagnosis of autoimmune hepatitis.

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 generally the alkaline phosphatase level. Although diseases that produce increased bilirubin levels are often called "cholestatic," it is important to remember that severe hepatocellular injury, as in acute hepatitis, also produces hyperbilirubinemia because of hepatocellular dysfunction. Causes of cholestasis are listed in Table 3.

Primary biliary cirrhosis usually occurs in middle-aged women who may complain of fatigue or pruritus. Primary sclerosing cholangitis has a strong association with ulcerative colitis. Patients with primary sclerosing cholangitis often are asymptomatic but may have jaundice, fatigue, or pruritus. Large bile duct obstruction often is due to stones or benign or malignant strictures. Remember that acute large bile duct obstruction from a stone may produce marked increases in aminotransferase levels. Intrahepatic mass lesions should be considered if a patient has cholestatic liver test abnormalities and a history of malignancy. Also, infiltrative disorders such as amyloidosis,

Table 2. 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	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

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

sarcoidosis, or lymphoma should be considered. A clue to a possible infiltrative disorder is 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 abnormalities. The abnormalities usually are 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. It is important to determine whether the increase is predominantly conjugated or unconjugated bilirubin. A common disorder that produces unconjugated hyperbilirubinemia (but not usually jaundice) is Gilbert's syndrome. Total bilirubin is generally less than 3.0 mg/dL, whereas direct bilirubin is 0.3 mg/dL or less. The level of bilirubin usually is higher when a patient is ill or fasting. A presumptive diagnosis of Gilbert's 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).

Table 3. 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/timing	Improvement after withdrawal of agent
Infiltrative disorder	History of malignancy, amyloidosis, sarcoidosis	Ultrasonography, computed tomography
Inflammation-associated	Symptoms of underlying inflammatory disorder	Blood cultures, appropriate antibody tests

ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

Patients with direct hyperbilirubinemia can be categorized as those with a nonobstructive condition and those with an obstructive condition. Abdominal pain, fever, or a palpable gallbladder (or a combination of these) is suggestive of obstruction. Risk factors for viral hepatitis, a bilirubin concentration greater than 15 mg/dL, and persistently high aminotransferase levels suggest that the jaundice is due to hepatocellular dysfunction. In patients with acute hepatocellular dysfunction, improvement in bilirubin concentration often lags behind the improvement in aminotransferase levels. A sensitive, specific, and noninvasive test to exclude an obstructive cause of jaundice is liver ultrasonography. In diseases characterized by large bile duct obstruction, the intrahepatic bile ducts generally are dilated, 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 despite normal-sized bile ducts on ultrasonography, the extrahepatic duct should be imaged with endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasonography.

GENERAL APPROACH TO ABNORMAL LIVER TESTS

When a patient has abnormal liver tests at presentation, it is helpful to classify the patient's condition as one of the clinical syndromes listed in Table 4, although the overlap among these categories is considerable. Patients with acute hepatitis or cirrhosis often have jaundice. The approach to patients with acute hepatitis, chronic hepatitis, cholestasis, and jaundice is outlined above. Patients with a "first-time" increase in liver enzyme levels are usually asymptomatic, and liver test abnormalities are found incidentally. As long as 1) no risk factors for liver disease are identified, 2) liver enzyme levels are less than three times normal, 3) liver function is preserved, and 4) the patient feels well, observation is reasonable, with the test repeated in a few months. If the repeat 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 for patients with incidentally discovered abnormal liver tests who are taking medications that only rarely cause liver disease.

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 with cirrhosis is similar to that of a patient with chronic hepatitis and cholestasis (as shown above). α_1-Antitrypsin deficiency, genetic hemochromatosis, and alcoholic liver disease frequently have cirrhosis as the first manifestation of liver disease. If a patient has clinical features that strongly suggest cirrhosis, confirmatory liver biopsy is not necessary.

ALGORITHMS FOR EVALUATING PATIENTS WITH ABNORMAL LIVER TESTS

Algorithms for evaluating patients who have abnormal liver tests are, at best, guidelines, and, at worst, misleading. Always remember that in evaluating (or not evaluating) abnormal liver tests, the patient's clinical presentation should be considered. Generally, a patient with liver test abnormalities that are less than twice normal may be followed as long as the patient is asymptomatic and the albumin level, prothrombin time, and bilirubin concentration are normal. Also, persistent abnormalities should be evaluated. Algorithms for evaluating increased levels of ALT, alkaline phosphatase, and conjugated bilirubin are shown in Figures 1 to 3.

Table 4. Abnormal Liver Tests: Clinical Syndromes

"First-time" increase in liver enzymes
Acute hepatitis
Chronic hepatitis
Cholestasis without hepatitis or jaundice
Jaundice
Cirrhosis or portal hypertension

MANAGEMENT OF FULMINANT LIVER FAILURE

Traditionally, *fulminant liver failure* has been defined as the presence of acute liver failure, including the development of hepatic encephalopathy, within 8 weeks after the onset of jaundice in a patient without a previous history of liver disease. Because not all patients with severe acute liver disease meet this strict definition, some authors have proposed the term *acute liver failure*, which encompasses other clinical scenarios, including fulminant liver failure. About 2,000 cases of fulminant liver failure occur annually in the United States. The overall mortality rate of fulminant liver failure without liver transplantation is high. Because many of the patients are young and previously healthy, the outcomes of this relatively unusual condition are particularly tragic. Specific management, including liver transplantation, is available, and knowledge of management strategies is important.

Determining the cause of fulminant liver failure is important for two 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 fulminant liver failure due to acetaminophen or hepatitis A is more than 50%; consequently, a more cautious approach would be advised before proceeding with liver transplantation. In comparison, spontaneous recovery from fulminant liver failure due to Wilson's disease is unusual and early liver transplantation would be recommended. Also, identifying a specific cause may have implications for other patients. The identification of a hepatotoxic agent is helpful in monitoring other patients receiving the same drug treatment. Identification of a viral cause of fulminant liver failure has implications for other patients who have been exposed to the transmissible agent. The US Acute Liver Failure Study Group has coordinated the effort of several centers that have attempted to better define the causes and outcome of acute liver failure in the United States. The most common identifiable causes are acetaminophen hepatotoxicity, idiosyncratic drug reactions, hepatitis A and B, and ischemia (Fig. 4).

The presenting symptoms of fulminant liver failure are usually those of acute hepatitis, including malaise, nausea, and jaundice. Portal systemic 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 5). Because

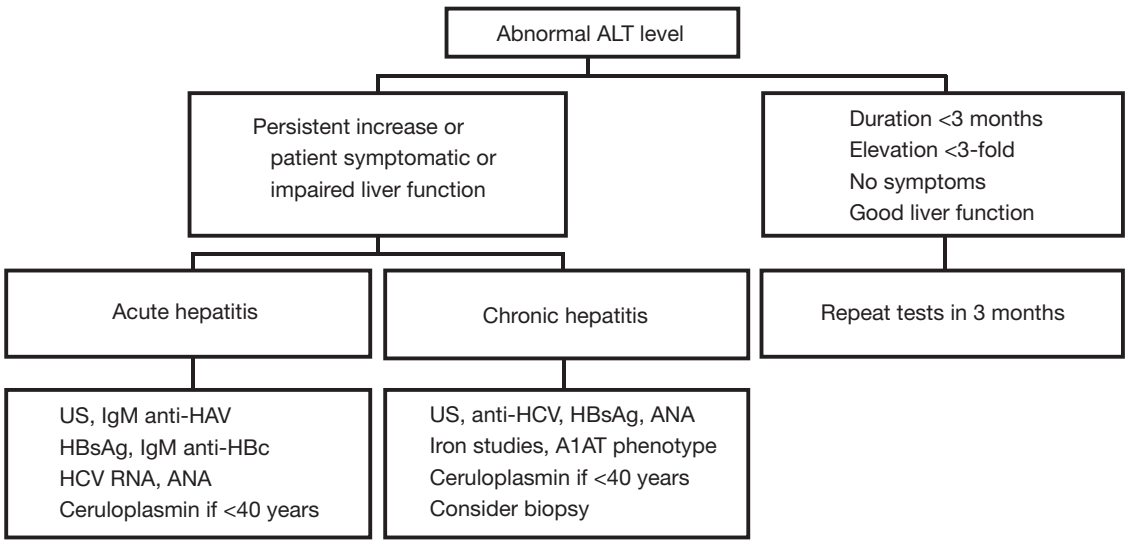

Fig. 1. Evaluation of abnormal alanine aminotransferase (ALT) level. A1AT, α_1-antitrypsin; ANA, antinuclear antibody; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; US, ultrasonography.

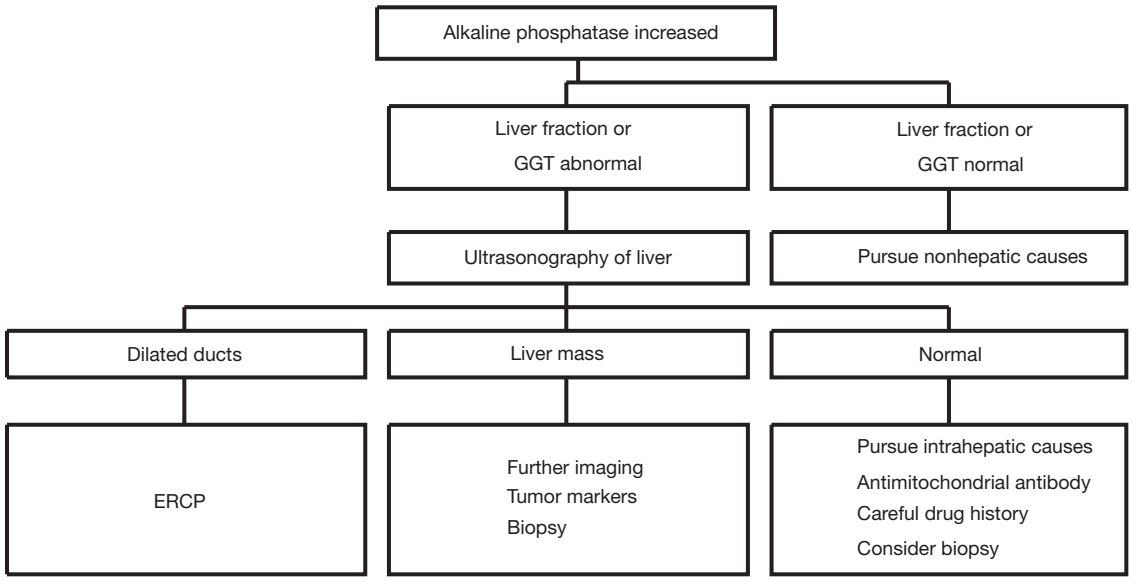

Fig. 2. Evaluation of increased alkaline phosphatase levels. ERCP, endoscopic retrograde cholangiopancreatography; GGT, γ-glutamyltransferase.

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 of fulminant liver failure are consistent with severe liver dysfunction. Aminotransferase levels are variably increased, although they usually are quite high. Fulminant Wilson's disease is characterized by only modest increases in aminotransferase levels and a normal or only minimally increased alkaline phosphatase level despite other, more typical laboratory evidence of liver failure. Evidence of hepatocellular

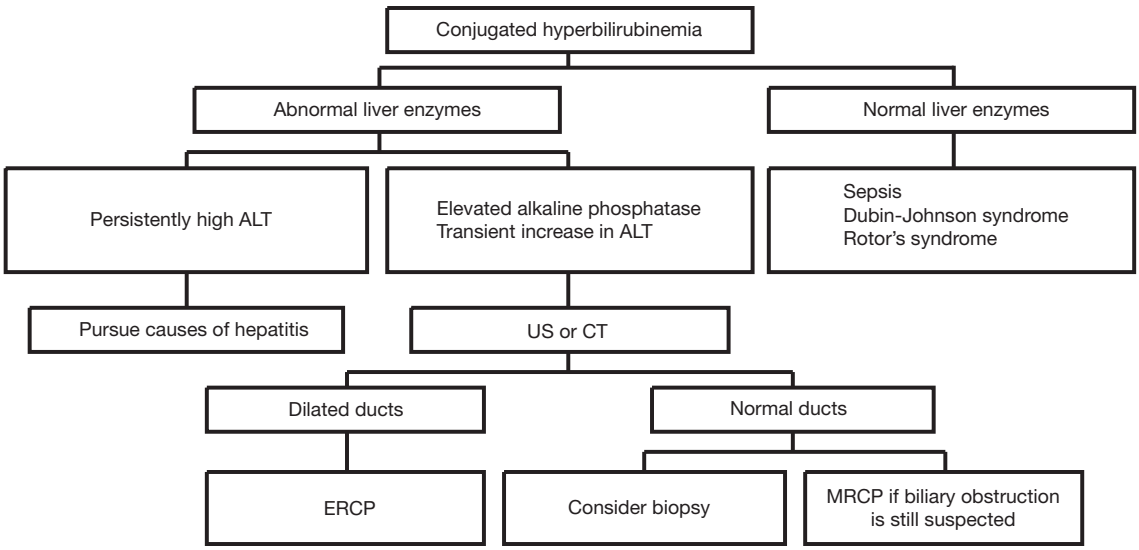

Fig. 3. Evaluation of conjugated hyperbilirubinemia. ALT, alanine aminotransferase; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; US, ultrasonography.

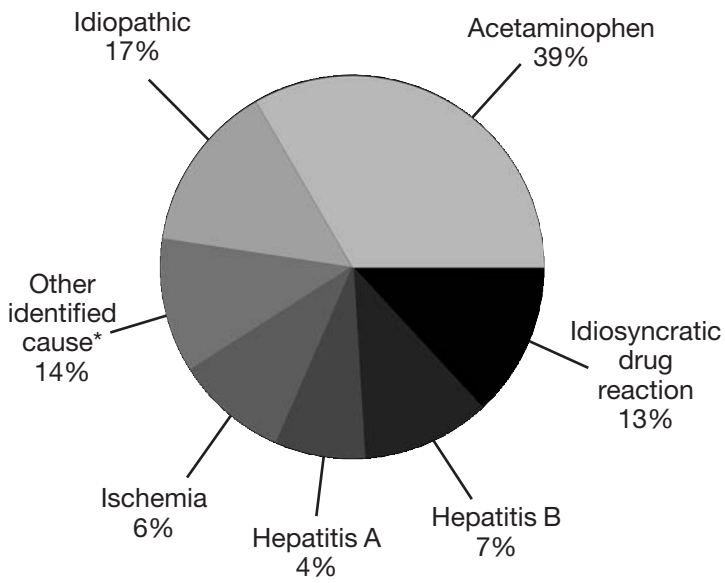

Fig. 4. Cause of fulminant liver failure in the United States, 1998-2001. *Includes autoimmune hepatitis, Wilson's disease, Budd-Chiari syndrome, pregnancy-associated, malignancy, heat stroke, sepsis, and giant cell hepatitis.

dysfunction includes a prolonged prothrombin time and high bilirubin concentration.

The encephalopathy associated with fulminant liver failure is likely different from that of chronic liver disease. The major difference is the propensity of encephalopathy of acute liver disease 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 an increase in the serum level of ammonia, although alterations in neurotransmitters likely are involved in causing mental status changes.

Cerebral edema is estimated to cause about 20% of deaths of patients with fulminant liver failure. Cerebral edema leads to death by causing brain ischemia and cerebral herniation.

Hypoglycemia is a frequent manifestation of fulminant liver failure, and the glucose level should be monitored carefully in all patients. The hypoglycemia is likely due to both inadequate degradation of insulin and diminished production of glucose by the diseased liver.

Infections are another common cause of death of patients with fulminant liver failure. Reasons for the infections are multiple but likely reflect severe illness and the need for numerous interventions and monitoring. The clinical features typical of infection, such as fever and leukocytosis, are not reliable in patients with fulminant liver failure. A high index of suspicion needs to be maintained, and any clinical deterioration should mandate a search for infection.

Table 5. 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, able to maintain sphincter tone
III	Sleeping most of the time, arousable to vocal stimuli, marked confusion, incoherent speech
IV	Comatose, unresponsive to pain, includes decorticate or decerebrate posturing

A hyperdynamic circulation and decrease in systemic vascular resistance frequently accompany fulminant liver failure. These features may be well tolerated by patients, but occasionally hemodynamic compromise can develop. Monitoring parameters may mimic sepsis. Fluid resuscitation often 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's disease, functional renal failure due to sepsis or hepatorenal syndrome, or acute tubular necrosis. Renal dysfunction may be more common when fulminant liver failure is due to acetaminophen hepatotoxicity. Monitoring of electrolytes, including sodium, potassium, bicarbonate, magnesium, and phosphorus, is important. Lactic acidosis also is common in fulminant liver failure, likely because of hypoperfusion and the inability of the diseased liver to clear lactate. The presence of acidosis is a risk factor for poor outcome in fulminant liver failure and has been incorporated into prognostic models.

Several models have attempted to predict outcome of fulminant liver failure. These have been developed to facilitate optimal timing of liver transplantation before the patient becomes so ill that transplantation is contraindicated. The most well known and widely used are the King's College criteria (Table 6). Liver transplantation likely improves mortality, but improved outcomes have been assessed only by comparison with historical controls.

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. It is especially important that sedatives be avoided at this point to allow close monitoring of mental status. Also, at most centers, 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 such monitors are used, all of which can be complicated by infection and bleeding. The goal of intracranial pressure monitoring is to allow treatment of high pressure and also to identify which patient is too ill for liver transplantation 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 tracheal suctioning, should be avoided or limited.

Table 6. King's College Criteria for Liver Transplantation in Fulminant Liver Failure*

1. Fulminant liver failure due to Wilson's disease or Budd-Chiari syndrome
2. Acetaminophen-induced if either of the following are met:
   a. pH <7.3 24 hours after overdose
   b. Creatinine >3.4 mg/dL and prothrombin time >100 seconds and grade 3-4 encephalopathy
3. Nonacetaminophen if either
   a. INR >6.5 *or*
   b. Any three of the following: INR >3.5, more than 7 days from jaundice to encephalopathy, indeterminate or drug-induced cause, age <10 years, age >40 years, bilirubin >17.5 mg/dL

INR, international normalized ratio.
**Any one of the three criteria.*

Paralyzing agents and sedatives may be necessary, although they may limit further assessment of neurologic status. For intracranial pressure more than 20 mm Hg or cerebral perfusion pressure less than 60 mm Hg, elevation of the head to 20 degrees, hyperventilation to a $Paco_2$ of 25 mm Hg, and mannitol (if renal function is intact) are advised. Barbiturate-induced coma or hypothermia 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 transplantation. A sudden decrease in intracranial pressure may indicate brain herniation.

The prolonged prothrombin time seen in patients with fulminant liver failure is a simple noninvasive measure to follow, and coagulopathy usually is not corrected unless there is bleeding or a planned intervention such as placement of a monitoring device. If bleeding occurs or an invasive procedure is necessary, fresh frozen plasma usually is administered first. Administration of platelets and fibrinogen may be necessary in certain circumstances. 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.

Liver transplantation has revolutionized the management of fulminant liver failure, which is the indication for 6% of liver transplants in the United States. Even though survival with transplantation for fulminant liver failure is lower than that for transplantation for other indications, outcomes are an improvement over the dismal survival rates for fulminant liver failure when prognostic criteria such as the King's College criteria indicate a poor outcome. Transplantation should be performed when a poor outcome is anticipated, yet before the patient has uncontrolled sepsis or prolonged periods of increased intracranial pressure that prevent recovery even with a functioning transplanted liver.

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CHAPTER 22

Chronic Viral Hepatitis

John J. Poterucha, MD

Viral infections are important causes of liver disease worldwide. The five primary hepatitis viruses that have been identified are A, B, C, D (or delta), and E. Other viruses such as cytomegalovirus or Epstein-Barr virus also can result in hepatitis as part of a systemic infection. In addition, medications, toxins, autoimmune hepatitis, or Wilson's disease may cause acute or chronic hepatitis.

It is useful to divide hepatitis syndromes into *acute* and *chronic* forms. *Acute hepatitis* can last from weeks up to 6 months and is often accompanied by jaundice. Symptoms of acute hepatitis tend to be similar regardless of the cause and include anorexia, malaise, dark urine, fever, and mild abdominal pain. Patients with *chronic hepatitis* are often asymptomatic but may complain of fatigue. Occasionally, they have manifestations of cirrhosis (ascites, variceal bleeding, or encephalopathy) as the initial presentation of 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. A more comprehensive discussion of acute hepatitis is found in other chapters. The primary hepatitis viruses are compared in Table 1, and the effects of the three most important viruses in the United States are summarized in Table 2.

HEPATITIS A

Epidemiology

The incidence of acute hepatitis A virus (HAV) infection is decreasing in the United States, although outbreaks still occur and HAV causes about 5% of cases of fulminant liver failure. The major 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, homosexual men, and perhaps persons who ingest raw shellfish. Outbreaks of HAV infection in communities are recognized frequently, although an exact source may not be found. The incubation period for HAV is 2 to 6 weeks.

Abbreviations: ALT, alanine aminotransferase; anti-HAV, antibody to hepatitis A virus; anti-HBc, antibody to hepatitis B core; anti-HBe, antibody to hepatitis B e; anti-HBs, antibody to hepatitis B surface; anti-HCV, antibody to hepatitis C virus; anti-HDV, antibody to hepatitis D 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; PCR, polymerase chain reaction.

Table 1. Comparison of the Four Primary Hepatitis Viruses

Feature	HAV	HBV	HDV	HCV
Incubation, days	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

HAV, hepatitis A virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus.

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 fulminant hepatitis that may require liver transplantation. 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 hepatitis A antibody (anti-HAV), which appears at the onset of the acute phase of the illness and disappears 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 and Prevention

The treatment of acute hepatitis A is supportive. Immune serum globulin should be administered to all household and intimate (including day care) contacts within 2 weeks after exposure. Hepatitis A vaccine should be offered to travelers to areas with an intermediate or high prevalence of hepatitis A, men who have sex with men, intravenous drug users, recipients of clotting factor concentrates, and patients with chronic liver disease. Widespread vaccination of health care workers or food handlers has not been advised.

HEPATITIS B

Epidemiology

Hepatitis B virus (HBV) is a DNA virus that causes about 30% of cases of acute viral hepatitis and 15% of cases of chronic viral hepatitis in the United

Table 2. Clinical Effect of Hepatitis Viruses in the United States*

	HAV	HBV	HCV
New infections per year	24,000	51,000	20,000
Fulminant, deaths/year	50	100	Rare
Chronic infections	0	1.25 million	3.2 million
Chronic liver disease, deaths/year	0	3,000-5,000	8,000-10,000

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.
**The Centers for Disease Control and Prevention estimates, 2005.*

States. Major risk factors for disease acquisition in the United States are sexual promiscuity and intravenous drug use. HBV infection is also common in Asia and Africa, where it usually is acquired perinatally or in early childhood. Many infected immigrants to the United States from high endemic areas probably acquired HBV by these routes.

Diagnostic Tests

A brief guide to serologic markers for hepatitis B is provided in Table 3. The interpretation of serologic patterns is found in Table 4. The best serologic test for acute hepatitis B is IgM antibody to hepatitis B core (anti-HBc). Occasionally, a patient with acute hepatitis B (usually with a severe presentation such as fulminant hepatitis) lacks hepatitis B surface antigen (HBsAg) and has only IgM anti-HBc as the marker for recent infection.

Sensitive tests for HBV DNA are now available. Nearly all patients with HBsAg have HBV DNA in serum when measured with a highly sensitive test such as the polymerase chain reaction (PCR). Commercially available tests now quantify HBV DNA. HBV DNA levels greater than 10^4 IU/mL generally are considered to indicate active viral replication. Also, lower levels in a patient with cirrhosis may be clinically important.

Occasionally, patients have IgG anti-HBc as the only positive hepatitis B serologic marker. This has several possible explanations. The most common reason in a low-risk population is a false-positive test (although the test is often repeatedly positive). Another explanation is a previous, resolved HBV infection in which the antibody to hepatitis B surface (anti-HBs) has decreased below the limit of detection. This can be documented indirectly 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 (sensitive assays such as PCR may be necessary) in the serum or liver.

The usefulness of serologic 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 (Fig. 1). 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.

Clinical Presentation and Natural History

The incubation period after HBV infection ranges from 30 to 160 days, and the clinical outcome varies. Acute hepatitis B in an adolescent or adult is icteric in about 30% of cases. Complete recovery with subsequent life-long immunity occurs in 95% of infected adults. About 5% of infected adults have persistence of HBsAg for longer than 6 months and are referred to as *chronically infected*. Immunosuppressed

Table 3. Hepatitis B Serologic Markers

Test	Significance
Hepatitis B surface antigen (HBsAg)	Current infection
Antibody to hepatitis B surface (anti-HBs)	Immunity (immunization or resolved infection)
IgM antibody to hepatitis B core (IgM anti-HBc)	Recent infection or "reactivation" of chronic infection
IgG antibody to hepatitis B core (IgG anti-HBc)	Remote infection
Hepatitis B e antigen (HBeAg) and/or HBV DNA $>10^4$ IU/mL	Active viral replication (high infectivity)

Table 4. 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 acute flare of chronic hepatitis B
-	+	-	+	-	±	-	Previous infection with immunity
-	+	-	-	-	-	-	Vaccination with immunity
+	-	-	+	-	+	$<10^5$	Hepatitis B inactive carrier state
+	-	-	+	+	-	$>10^5$	Chronic hepatitis B
+	-	-	+	-	+	$>10^5$	HBeAg-negative chronic hepatitis B (often "precore" or "core promoter" variants)

Anti-HBe, antibody to hepatitis B e; anti-HBs, antibody to hepatitis B surface; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgG anti-HBc, IgG antibody to hepatitis B core; IgM anti-HBc, IgM antibody to hepatitis B core.

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 may present in one of four phases (Fig. 2). An immune tolerant phase is recognized in many patients who are infected perinatally. This phase is characterized by normal levels of alanine aminotransferase (ALT), presence of hepatitis B e antigen (HBeAg), and very high HBV DNA levels. Generally, liver

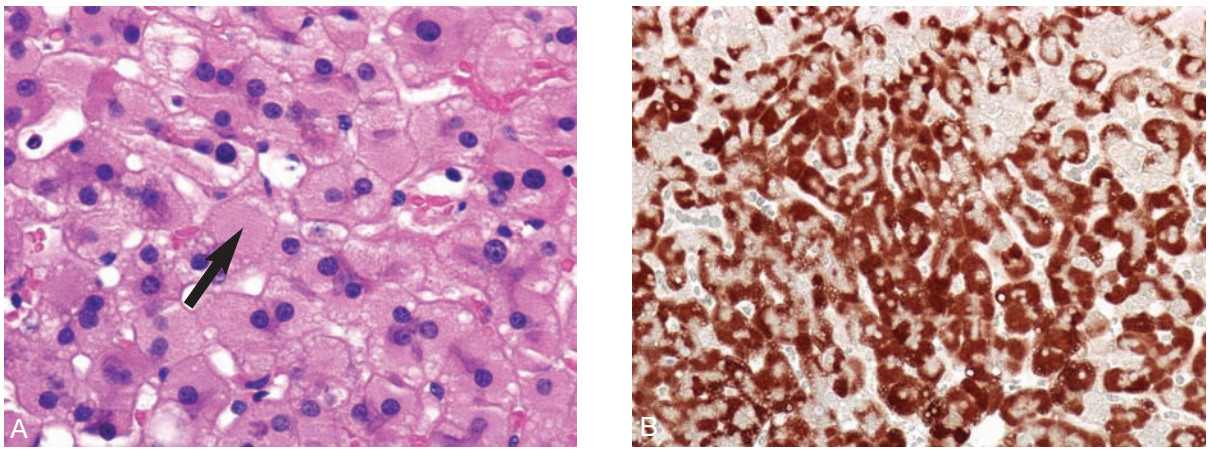

Fig. 1. Liver biopsy specimen from patient with hepatitis B. *A*, Ground-glass hepatocyte (*arrow*). (Hematoxylin-eosin.) *B*, Immunostain for hepatitis B surface antigen showing positive staining of hepatocyte cytoplasm.

biopsy specimens from these patients show minimal changes except for ground-glass hepatocytes. The immune tolerant phase can last up to the age of 40 years and generally evolves under immune pressure into the *HBeAg-positive chronic hepatitis B phase*, characterized by increased ALT levels, the presence of HBeAg, and more than 10^4 IU/mL of HBV DNA. Active inflammation and often fibrosis are seen in liver biopsy specimens. This phase generally is thought to lead to progressive liver damage, including cirrhosis and an increased risk of hepatocellular carcinoma. 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 anti-HBe (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. Most patients remain in this phase for many years and have a better prognosis than those with active liver inflammation and viral replication.

About one-third of inactive carriers have a reactivation of chronic hepatitis characterized by abnormal ALT levels and HBV DNA of more than 10^4 IU/mL. This may be associated with a recurrence to the HBeAg-positive state, but more commonly it is due to a precore or core promoter variant that produces HBeAg-negative chronic hepatitis B. This *HBeAg-negative chronic hepatitis B phase* is associated with progression of liver damage and, perhaps, an increased risk of hepatocellular carcinoma. Patients with HBeAg-negative chronic hepatitis B are more likely to have lower DNA levels and 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 aminotransferase 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 5. Because disease activity changes in patients with chronic hepatitis B, even after years of senesence, periodic monitoring with liver tests and hepatitis B markers is necessary.

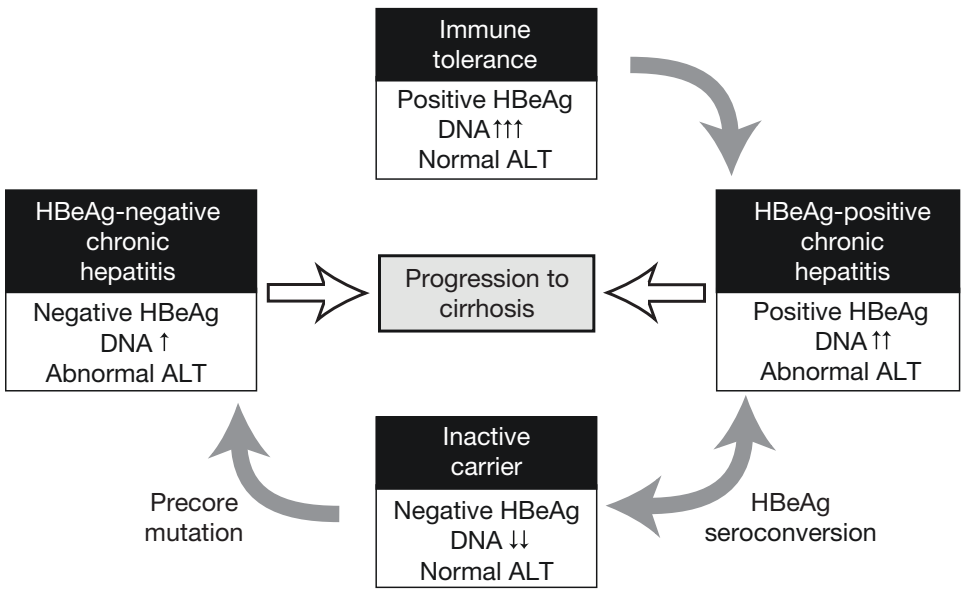

Fig. 2. Phases of chronic hepatitis B virus infection. *White arrows*, changes of histopathology; *gray arrows*, changes in serologic markers between phases. *Up-* and *down-facing arrows*, an increase or decrease of DNA level (↑ = low increase; ↑↑ = moderate increase; ↓↓ = moderate decrease; ↑↑↑ = high increase). ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen. (From Pungpapong S, Kim WR, Poterucha JJ. Natural history of hepatitis B virus infection: an update for clinicians. Mayo Clin Proc. 2007;82:967-75. Used with permission of Mayo Foundation for Medical Education and Research.)

HBsAg clears spontaneously in about 1% of chronically infected patients annually, although this rate is lower in endemic areas where HBV is acquired at a very young age.

Overall, about 15% to 40% of patients with chronic HBV infection develop serious sequelae of the disease, either by the development of decompensated liver disease or hepatocellular carcinoma. Factors associated with the development of cirrhosis are older age, infection with hepatitis C virus (HCV), human immunodeficiency virus (HIV), or hepatitis D virus (HDV), genoype 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 for the development of hepatocellular carcinoma.

Patients with chronic hepatitis B and cirrhosis are at high risk for the development of hepatocellular carcinoma, and surveillance with ultrasonography and α-fetoprotein every 6 to 12 months is advised. Surveillance should be considered also for patients without cirrhosis who meet one of the following criteria: family history of hepatocellular carcinoma, Asian male older than 40 years, Asian female 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.

Eight hepatitis B genotypes have been identified. These are labeled A though H. The hepatitis B genotype is determined largely by the country in which infection is acquired. All genotypes have been identified in the United States. The clinical significance of various hepatitis B genotypes is still being studied, and, clinically, the hepatitis B genotype is not commonly used. In Asian patients, genotype B has a better prognosis than genoytpe 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. Genotypes A and B may have a better response to peginterferon therapy than other genotypes.

Treatment

Generally, hepatitis B is treated if the patient is at risk for disease progression. This includes patients who have liver enzyme levels more than twice the upper limit of normal, active viral replication (as defined by HBV DNA more than $10^{4\text{-}5}$ IU/mL), and active disease identified in liver biopsy specimens. Defining a specific HBV DNA level that warrants treatment is difficult because some patients with advanced and active disease have relatively low levels and others, especially those in the immune tolerant phase, have very high levels despite the lack of disease activity. In general, a value greater than 20,000 IU/mL is used as an indication for treatment; however, in the presence of cirrhosis or HBeAg-negative chronic hepatitis, a level higher than 2,000 IU/mL has been proposed as an indication for treatment.

Liver biopsy is not always necessary but can be helpful in patients who otherwise do not meet clear

Table 5. 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 immune suppression	Chemotherapy, antirejection therapy, corticosteroids
Induced by antiviral therapy	Interferon (common), oral agents (rare)
Superimposed infection with other viruses, especially hepatitis D virus	Exposure to hepatitis D (usually due to illicit drug use), A, or C
Other causes of acute hepatitis	History of alcohol excess, medications, illegal drugs

Anti-HBc, antibody to hepatitis B core; HBeAg, hepatitis B e antigen.

criteria for treatment. Liver biopsy also can be used to diagnose cirrhosis, which could mandate a change in management, such as evaluation for esophageal varices or surveillance for hepatocellular carcinoma.

Hepatitis B can be treated with interferon or one of the oral agents (lamivudine, adefovir, entecavir, or telbivudine). Peginterferon has replaced standard interferon because of once-weekly dosing and perhaps better efficacy. 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, 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-Pugh class B or C cirrhosis should not be treated with interferons because of the risk of precipitating decompensation with this flare. Side effects of peginterferon are common and are considered below (HEPATITIS C).

The oral agents are the drugs prescribed most frequently for the treatment of chronic hepatitis B. They are compared in Table 6. These drugs are remarkably free of side effects, although occasionally adefovir can cause nephrotoxicity. The oral agents 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. Treatment with lamivudine or telbivudine is complicated by resistant mutations at a rate of about 10% to 15% per year. Resistance to adefovir occurs at a rate of about 1% to 4% per year. Resistance to entecavir is uncommon unless the patient has previously developed resistance to lamivudine, although data for long-term treatment are needed. Adefovir and entecavir are effective against lamivudine-resistant strains, although adefovir is probably a better choice because of a higher rate of resistance when entecavir is given to patients with resistance to lamivudine. For these patients, adefovir should be added to lamivudine. About 15% to 20% of patients treated with oral agents have seroconversion of HBeAg after 1 to 2 years of therapy, and 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 occurs only rarely and is not a reasonable treatment goal.

The choice of therapeutic agent for hepatitis B depends on several factors. As noted above, only active hepatitis should be treated. 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 side effects of the drug. The oral agents are preferred for patients with cirrhosis, particularly if there is evidence of decompensation. Patients with long-standing hepatitis B, such as adults who acquired the disease in the perinatal period, are not likely to have a response to peginterferon treatment, and the oral agents are preferred. Oral agents are preferred also for patients who are immunosuppressed, for example, after organ transplantation or infection with HIV. Patients with hepatitis B who need a course of chemotherapy have an increased risk of disease flare, and treatment with one of the oral agents is advised. Treatment should be given not only during the course of chemotherapy but for 6 months after therapy has been completed.

For patients with end-stage liver disease due to hepatitis B, liver transplantation is advised. Listing for transplantation is recommended when a patient has seven Child-Pugh points or hepatocellular carcinoma complicating cirrhosis. Patients with hepatitis B who have HBeAg or high HBV DNA levels (or both) before liver transplantation are at particularly high risk for recurrence after transplantation. For these patients, oral agents are recommended before transplantation and a combination of hepatitis B immunoglobulin and an oral agent after transplantation. Even in patients without active viral replication, recurrence rates are sufficiently high that both preoperative and postoperative therapy with one of the oral agents is still given by most transplant groups.

Prevention

Hepatitis B immunoglobulin should be given to household and sexual contacts of patients with acute hepatitis B. Infants and previously unvaccinated 10- to 12-year-old children (who are reaching the age when they will be at highest risk for acquiring disease) should receive hepatitis B vaccine. The marker of immunity is anti-HBs.

Table 6. Oral Agents for Treatment of Hepatitis B

Feature	Agent			
	Lamivudine	Adefovir	Entecavir	Telbivudine
Cost per month, $US	230	630	720	500
HBeAg seroconversion, % of patients	20	12	21	22
Loss of HBV DNA, % of patients	40	21	67	60
Resistance, patients	20% at 1 year	0 at 1 year	Naïve: <1% at 2 years	4% at 1 year
	70% at 5 years	29% at 5 years	Lamivudine resistance: 7% at 1 year	21% at 2 years
Durability of response, % of responding patients	50-80	90	69	80

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

Neonates often acquire hepatitis B perinatally if the mother is infected. Because infected neonates are at high risk for the development of chronic infection, HBsAg testing should be performed on all pregnant women. If a pregnant woman is HBsAg-positive, the infant should receive both hepatitis B immunoglobulin and hepatitis B vaccine.

HEPATITIS D

HDV (or the delta agent) is a defective virus that requires the presence of HBsAg to replicate. Consequently, there is no reason to search for HDV unless HBsAg is present. HDV infection can occur simultaneously with HBV (coinfection) or as a superinfection in persons with established hepatitis B. Hepatitis D is diagnosed by antibodies to HDV (anti-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.

HEPATITIS C

HCV is the cause of the most common chronic blood-borne infection in the United States. It has been estimated that 3 to 4 million Americans are infected with the virus; about 70% of them have abnormal ALT levels. Although the number of new cases of HCV infection is decreasing, the number of deaths is increasing 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 transplantation.

Diagnostic Tests

Antibodies to HCV (anti-HCV) indicate exposure to the virus and are not protective. The presence of anti-HCV can indicate either current infection or a previous infection with subsequent clearance. Even after clearance of the infection, only about 10% of patients lose anti-HCV. The presence of anti-HCV in a patient who has an abnormal ALT level and risk factors for acquiring hepatitis C is strongly suggestive of current HCV infection. The initial test for identifying anti-HCV is enzyme-linked immunoassay. False-positive results for anti-HCV by this test are unusual but can occur in patients with hypergammaglobulinemia (eg, patients with autoimmune hepatitis). The specificity (but not sensitivity) of enzyme-linked immunoassay for anti-HCV is improved with the addition of the recombinant immunoblot assay for anti-HCV. A

guide to the interpretation of anti-HCV tests is provided in Table 7.

The "gold standard" for the diagnosis of hepatitis C infection is the presence of HCV RNA in serum as determined with PCR. Most reference laboratories are able to reproducibly perform this HCV RNA assay with a sensitivity limit of 10 to 50 IU/mL. HCV RNA by PCR is now the preferred next test (bypassing anti-HCV by recombinant immunoblot assay) for patients with abnormal liver enzyme levels or for those at high risk for HCV infection who are found to be anti-HCV–positive by enzyme-linked immunoassay.

Levels of HCV RNA do not correlate with disease severity or prognosis, and the major use of quantitative assays is to stratify response to therapy. Patients with viral levels higher than 600,000 IU/mL are less likely to have a response to treatment. The determination of HCV genotype is helpful in assessing the likelihood of treatment response. Patients with HCV genotype 1 (which comprises about 70% of US patients) are less likely to have a response to therapy than those with genotype 2 or 3. Liver biopsy is not necessary for the diagnosis of hepatitis C, but it is helpful in assessing the severity of disease for prognostication and in making decisions about treatment and screening. Typical biopsy findings include a mononuclear (predominantly lymphocytic) portal hepatitis with lymphoid follicles and mild steatosis (Fig. 3).

Table 7. Interpretation of Anti-HCV Test Results

Anti-HCV		
By EIA	**By RIBA**	**Interpretation**
+	-	False-positive EIA, patient does not have true antibody
+	+	Patient has antibody*
+	Indeterminate	Uncertain antibody status

Anti-HCV, antibody to hepatitis C virus; EIA, enzyme-linked immunoassay; RIBA, recombinant immunoblot assay.
**Anti-HCV does not necessarily indicate current HCV infection (see text).*

Clinical Presentation and Natural History

The incubation period of HCV ranges from 2 to 23 weeks (mean, 7.5 weeks). Infection with HCV rarely presents clinically as 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, 60% to 85% develop chronic infection (Fig. 4). 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 correlates poorly with the histologic severity of disease. Some patients have fatigue or vague right upper quadrant pain (or both). Patients also may come to attention because of complications of end-stage liver disease or, rarely, extrahepatic complications such as cryoglobulinemia or porphyria cutanea tarda. Patients with hepatitis C-associated cryoglobulinemia usually have a vasculitic rash of the lower extremities, but they also may have a membranoproliferative glomerulonephritis or polyneuropathy. The cryoglobulinemia and its associated complications usually respond to the treatment of hepatitis C. Porphyria cutanea tarda is manifested as a rash on sun-exposed areas, particularly the back of the hands. Many patients also have abnormal iron test

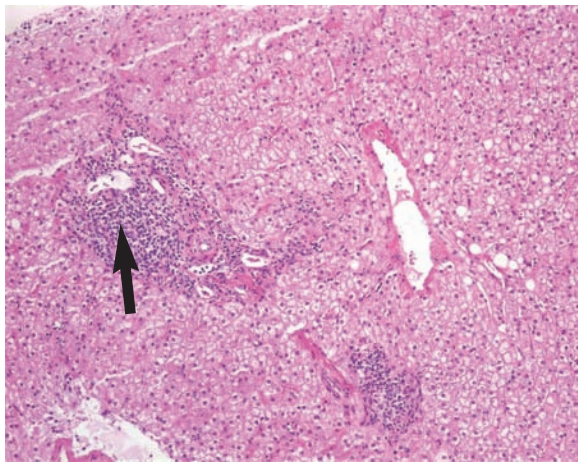

Fig. 3. Biopsy specimen from patient with hepatitis C. Note portal infiltrate, lymphoid follicle (*arrow*), and mild steatosis.

results. The response of porphyria cutanea tarda to anti-hepatitis C therapy is more uncertain than the response of cryoglobulinemia. Phlebotomy improves the rash of porphyria cutanea tarda and generally is considered first-line therapy.

Up to 30% of patients chronically infected with HCV have a persistently normal level of ALT. These patients generally have less aggressive histologic features and a lower risk of disease progression than do patients with hepatitis C and abnormal ALT levels. The role of liver biopsy and the treatment of hepatitis C in patients who have normal ALT levels are debated, but most hepatologists manage patients who have normal ALT levels similarly to those who have abnormal ALT levels.

Nearly all mortality and most morbidity associated with hepatitis C are due to cirrhosis. About 20% to 30% of patients with chronic hepatitis C develop cirrhosis over a 10- to 20-year period (Fig. 4). Multiple factors have been studied to identify the subgroup of patients likely to develop progressive liver disease. Important factors 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.

Perhaps the most important predictive factor for the development of cirrhosis is the severity of the histologic features of the liver at presentation. Histologic specimens need to be interpreted with knowledge of the duration of infection (if known). Patients who have only mild portal hepatitis without fibrosis despite 20 years of infection have a significantly lower risk of progression than those who have more active disease with a similar duration of infection. Histologic markers of more active disease include moderate degrees of inflammation and necrosis and the presence of periportal or septal fibrosis. Liver biopsy should be performed in most patients being considered for treatment of hepatitis C to assist in decisions about treatment.

Treatment

The mortality and morbidity of chronic hepatitis C are related largely to cirrhosis. Consequently, treatment clearly is indicated for patients who are at highest risk for the development of cirrhosis: an anticipated long duration of hepatitis C, a history of alcohol use, or active disease with at least periportal fibrosis seen in liver biopsy specimens. Patients who have a high probability of having a response to treatment, such as those with genotype 2 or 3, may be considered candidates for treatment regardless of liver biopsy findings. Thus, biopsy is not always necessary before treatment. Knowing whether the patient has cirrhosis is necessary for monitoring for the development of esophageal varices and hepatocellular carcinoma. For patients with clear evidence of portal hypertension, biopsy is not needed to confirm cirrhosis. Therapy also

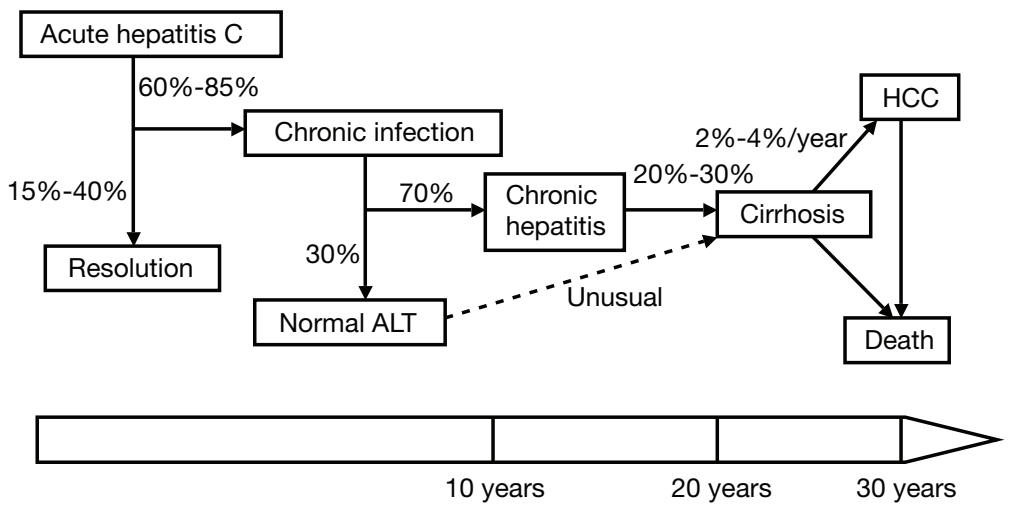

Fig. 4. Natural history of hepatitis C. ALT, alanine aminotransferase; HCC, hepatocellular carcinoma. Percentage values refer to patients.

should be offered to patients who have extrahepatic manifestations of hepatitis C, such as vasculitis related to cryoglobulinemia. In addition, patients who have an anticipated long lifespan, for example, those younger than 40 years, might be offered treatment independently of liver biopsy findings or genotype. Treatment may be indicated to reduce potential transmission, for example, a health care worker who performs invasive procedures.

Currently, peginterferon in combination with ribavirin is the standard of care for patients with hepatitis C who are deemed candidates for treatment. This combination therapy, given for 6 to 12 months, results in a sustained clearance of HCV RNA from serum in about 55% of patients. Baseline variables associated with a sustained response to combination therapy include HCV genotype 2 or 3, HCV RNA levels less than 800,000 IU/mL, no or only portal fibrosis, female sex, and age younger than 40 years. Patients who receive at least 80% of the planned dose of peginterferon and ribavirin for the duration of therapy are more likely to have a response. Adherence to therapy is particularly important for harder-to-treat patients, such as those with genotype 1.

Hepatitis C genotype and viral level should be determined before treatment is initiated. When treating patients who have genotype 1 or 4, the HCV RNA level should be determined after 12 weeks of therapy (Fig. 5). Patients who do not achieve a 2 $\log_{10}$ decrease in HCV RNA level from the pretreatment value have a very low rate of sustained response, and treatment may be discontinued. Those with a 2 $\log_{10}$ decrease (or are HCV RNA-negative) at 12 weeks should continue to receive treatment, and HCV RNA level determined at 24 weeks. Those who are HCV RNA-positive at 24 weeks will not achieve a sustained response, and treatment can be stopped. Patients who are HCV RNA-negative at 24 weeks should complete a total of 48 weeks of treatment.

Patients with genotype 2 or 3 have a high rate of response, and determining the HCV RNA level at 12 weeks probably is not cost-effective (Fig. 6). If therapy is tolerated poorly and a decision needs to be made about continuing therapy, the 12-week stop rule described for genotype 1 may be applied. Otherwise, treatment should be continued for a total of 24 weeks.

The most troublesome side effects of hepatitis C therapy are hematologic and neuropsychiatric. Anemia is the most common reason for prematurely discontinuing hepatitis C combination therapy. Ribavirin causes a dose-dependent, reversible hemolysis that is evident within 4 weeks after treatment is initiated. Peginterferon, because of its bone-marrow–suppressive effects, interferes with erythropoiesis that may otherwise compensate for the ribavirin-induced hemolysis. Fatigue, dyspnea, or symptoms of cardiovascular disease may accompany anemia. Because ribavirin-induced hemolysis is dose-dependent, dose reduction usually improves the hemoglobin level, but perhaps at the expense of treatment efficacy.

Erythropoietin has been used to maintain hemoglobin levels (and therefore ribavirin doses) in patients treated for hepatitis C. Whether erythropoietin-induced improvements in hemoglobin level and ribavirin dosing will lead to improved hepatitis C response rates has not been demonstrated. Patient age, symptoms associated with anemia, risk factors for or presence of cardiovascular disease, and body size should be considered when deciding whether to use erythropoietin.

Neutropenia that occurs during hepatitis C therapy is due to peginterferon. An absolute neutrophil count less than 500 cells/mL is rare. Serious infections are extremely rare except perhaps in patients with other risk factors for infection, for example, decompensated cirrhosis. Consequently, neutropenia seldom requires intervention in patients receiving peginterferon therapy.

Most neuropsychiatric side effects of hepatitis C therapy are due to peginterferon, although anemia and other side effects of ribavirin may potentiate symptoms. The prevalence of neuropsychiatric side effects among patients with hepatitis C is high even before treatment, and baseline mood status may influence the likelihood of dose-limiting neuropsychiatric manifestations of interferon. Pretreatment education for patients and family members about the potential for these side effects is helpful. Reassurance is also important because many patients are able to cope with the neuropsychiatric manifestations by realizing that they are related to treatment and will resolve once treatment has been discontinued. Nevertheless, 30% of patients treated for HCV infection require

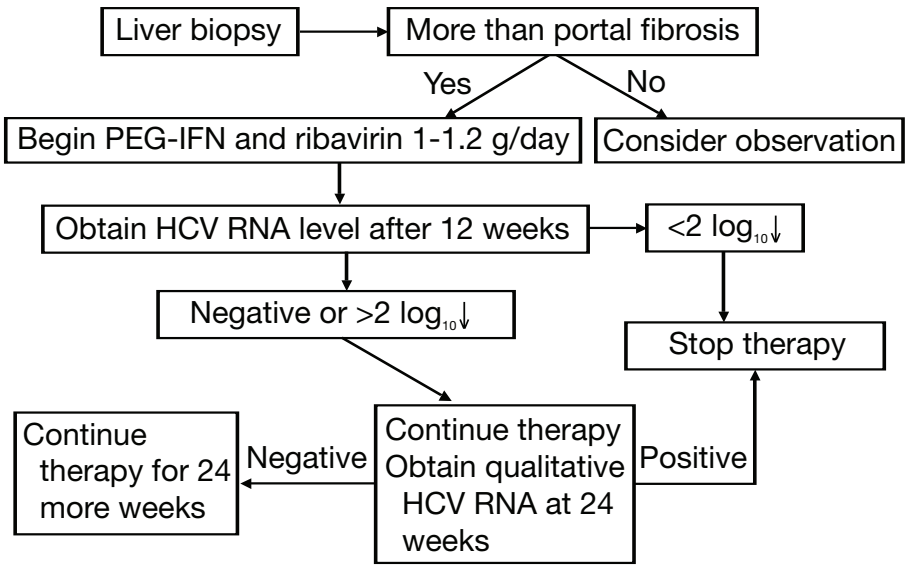

Fig. 5. Management of HCV genotype 1. HCV, hepatitis C virus; PEG-IFN, peginterferon.

the introduction or addition of medications for the treatment of these side effects.

Patients who develop suicidal ideation while receiving treatment should discontinue therapy and be referred to psychiatry. For patients with notable depression without suicidal ideation, a selective serotonin reuptake inhibitor such as citalopram can be prescribed. For patients with a prominent anxiety or irritability component of depression, a less activating selective serotonin

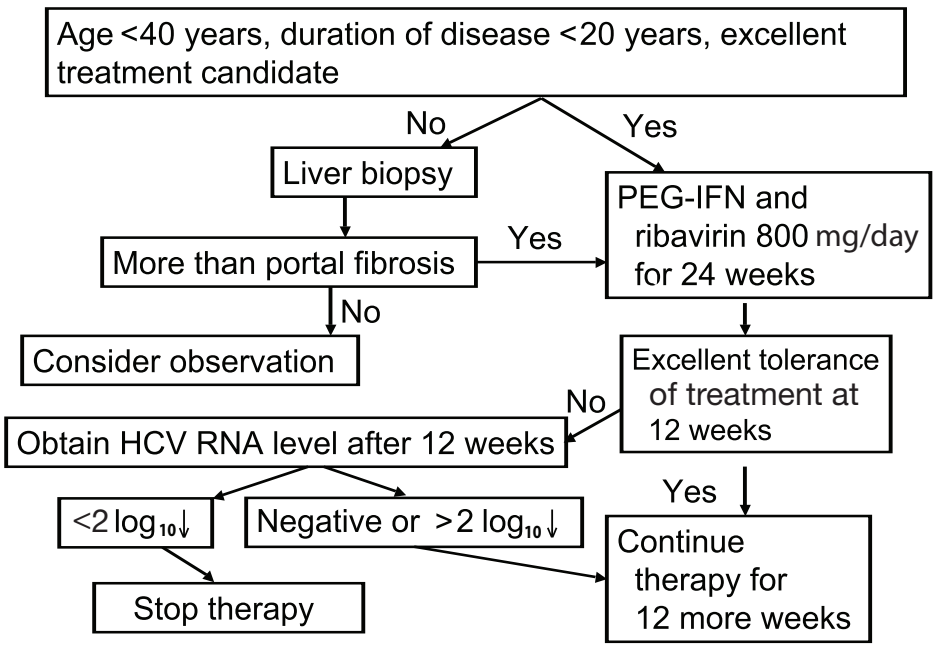

Fig. 6. Management of HCV genotype 2 or 3. HCV, hepatitis C virus; PEG-IFN, peginterferon.

reuptake inhibitor such as paroxetine, fluvoxamine, or mirtazapine may be helpful. Mirtazapine is also useful for patients who have considerable weight loss with interferon therapy. Fluoxetine, sertraline, venlafaxine, and bupropion are more activating and, thus, may be preferred for patients who have fatigue or cognitive slowing. Patients who have persistent depression despite treatment with antidepressants are referred to psychiatry.

Patients who are not candidates for treatment should be evaluated annually with routine liver tests. For those with early-stage disease, a repeat liver biopsy in 3 to 5 years may be indicated to assess for histologic progression. Patients with cirrhosis are at increased risk for hepatocellular carcinoma, particularly if they have a history of alcohol excess. The risk of hepatocellular carcinoma complicating hepatitis C with cirrhosis is 1.4% to 4% per year. Screening with α-fetoprotein and liver ultrasonography every 6 to 12 months is advised for patients with cirrhosis who are candidates for treatment of hepatocellular carcinoma with liver transplantation, liver resection, or percutaneous ablation.

Patients with hepatitis C and cirrhosis (including those with hepatocellular carcinoma) should be considered for liver transplantation. Currently, patients with seven Child-Pugh points are eligible for listing and should be referred for liver transplantation if there are no contraindications. For patients who received a liver transplant for hepatitis C, post-transplant 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 transplantation in the United States.

Prevention

No vaccine is available for hepatitis C. Transmission by needlestick injury is unusual, although monitoring after inadvertent exposure is advised. Baseline anti-HCV testing with subsequent determination of HCV RNA level 4 weeks after exposure is recommended. Documented acute infections probably should be treated to prevent chronic infection. Perinatal exposure is also uncommon, but it may be more likely if the mother is also infected with 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, donation of blood 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. Physicians in the United States are unlikely to have a patient with hepatitis E. Rarely, a patient may become infected during foreign travel. 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. Patients with HIV infection are at increased risk for remaining chronically infected after the acute infection compared with HIV-negative patients. HIV-infected patients with HBV infection have higher HBV DNA levels and increased liver mortality than HBV patients without HIV infection.

The response to treatment for HBV infection with interferon in HIV-infected patients is very low, and treatment with oral agents generally is advised. Lamivudine is a logical choice for patients who require treatment for HIV infection. The combination of tenofovir and emtricitabine is also a logical choice because it has an antiviral effect on both HIV and HBV. For the rare patient who requires treatment for 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, HCV/HIV-infected patients have higher HCV RNA levels, increased risk of vertical and sexual transmission of HCV, an increased risk of cirrhosis, and an increased risk of hepatocellular carcinoma. Patients with HCV/HIV should be considered for treatment. The HIV disease should be controlled, and treatment is generally recommended only if the HIV level is less than 1,000 copies/mL and the CD4 count more than 200 μL. The patient should have no recent opportunistic infections, and most physicians advocate liver biopsy before treatment. Patients with stage 0 or stage 1 fibrosis generally can be observed unless they are HCV genotype 2 or 3.

The doses used to treat hepatitis C in HCV/HIV-infected patients are similar to those used for treating HCV infection in patients without HIV infection. Twelve months of treatment is better than 6 months, even for patients with HCV genotype 2 or 3. Three-month and 6-month "stop" rules are used to help identify nonresponders. Erythropoietin and antidepressants are often necessary to maintain dosing.

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CHAPTER 23

Clinical Approach to Liver Mass Lesions

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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 (Table 1).

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 highly valuable in the differential diagnosis of liver masses.

A history of 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

Abbreviations: CA19-9, carbohydrate antigen 19-9; 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; PET, positron emission tomography; PSC, primary sclerosing cholangitis; PTC, percutaneous transhepatic cholangiography; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Table 1. Clinial 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

growing mass can reach a substantial size that almost completely occupies the liver without causing noticeable symptoms. It may only come to attention when the mass becomes a visible abdominal protuberance (Fig. 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 appear as the sudden onset of severe abdominal pain. This is most typical of benign hepatic adenomas or hepatocellular carcinomas, which characteristically are extremely vascular. If 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 viral, alcoholic, nonalcoholic steatohepatitis, autoimmune, metabolic, or other causes of cirrhosis are at increased risk for the development of 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 with cirrhosis of any cause or who acquired chronic HBV infection at birth or in early life to be entered into a regular program of surveillance with liver ultrasonography, with or without serum α-fetoprotein measurements, 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 (Fig. 2). Persons with a family history of hepatocellular carcinoma and those with high HBV viral loads and active chronic hepatitis should also have regular surveillance.

Primary sclerosing cholangitis (PSC), 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 PSC can presage the development of cholangiocarcinoma. More than half of the cholangiocarcinomas that occur in patients with PSC will be diagnosed within 2 years after the initial diagnosis of PSC; 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

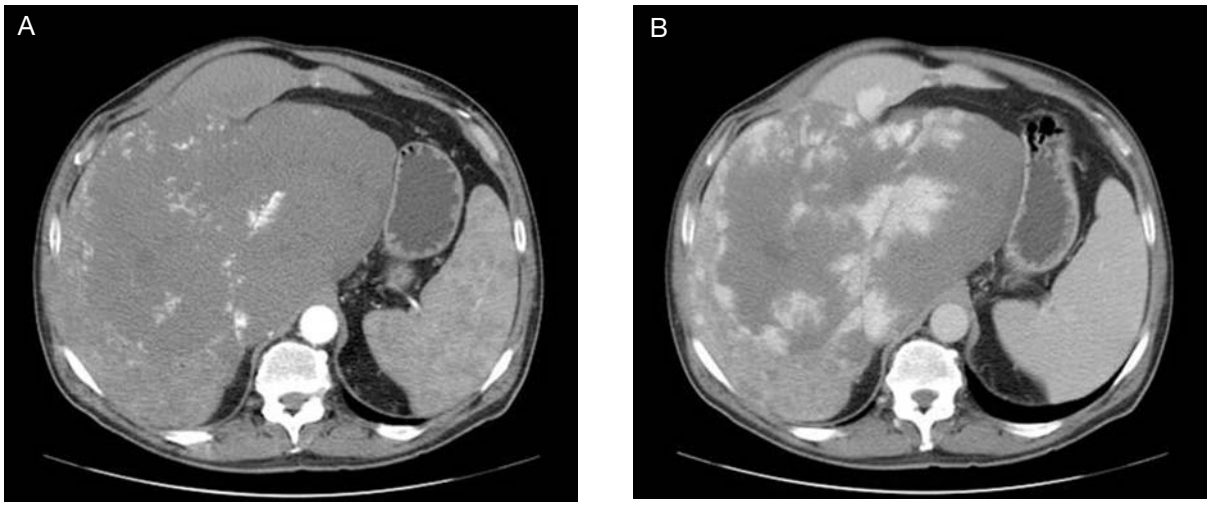


Fig. 1. Large cavernous hemangioma with the presentation of an abdominal mass. *A*, Arterial phase with peripheral nodular enhancement. *B*, Venous phase with fill-in of contrast from the periphery toward the center of the mass.

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.

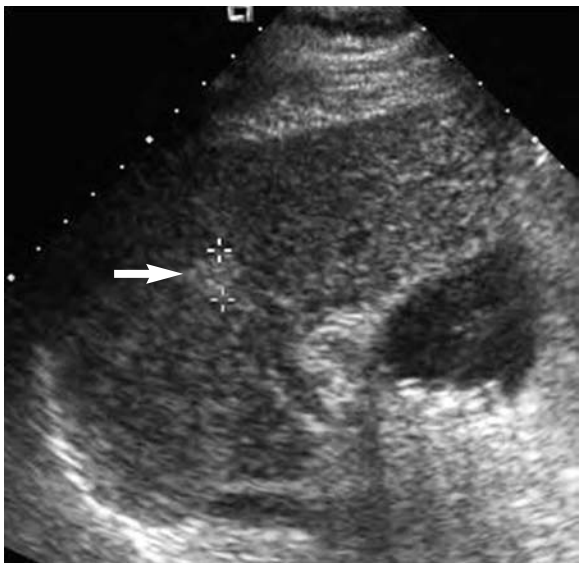


Fig. 2. A small 1.3-cm mass (*arrow*) identified in an at-risk patient during ultrasonographic screening for hepatocellular carcinoma.

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 a caput medusa 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 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, with tense ascites causing compression of the inferior vena cava and loss of intravascular oncotic pressure due to hypoalbuminemia, or it may be nonspecific, due to 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 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 in 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 level of albumin is often low and the prothrombin time increased in patients with cirrhosis. Tests that identify the specific cause, 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 α-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 α-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), and various nuclear imaging studies, including tagged red cell studies (for cavernous hemangiomas), technetium 99m sulfur colloid imaging (to distinguish focal nodular hyperplasias from adenomas), 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, ferumoxide (Feridex), an injectable solution of superparamagnetic iron oxide, is taken up by reticuloendothelial cells in the liver, whereas tissues such as tumors with decreased reticuloendothelial cell function retain their signal intensity. Thus, ferumoxide is considered a "negative" contrast agent (the liver decreases in signal intensity, not the lesion). Another newer paramagnetic MRI contrast agent, gadobenate dimeglumine (MultiHance), undergoes biliary as well as renal excretion and behaves as a nonspecific gadolinium chelate in the first minutes after administration and as a liver-targeted agent in later delayed phases; this allows further delineation of lesion characteristics in MRI scans obtained 60 to 120

minutes after the injection of contrast and can be particularly helpful in distinguishing between focal nodular hyperplasias and adenomas.

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 1.5-5:1 female-to-male predominance, being 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 hyperplasias.

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

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 filling-in toward the center of the lesion (Fig. 3).

MRI with gadolinium contrast—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.

Technetium 99m-labeled red blood cell scintigraphy—This can be used to confirm the diagnosis in 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.

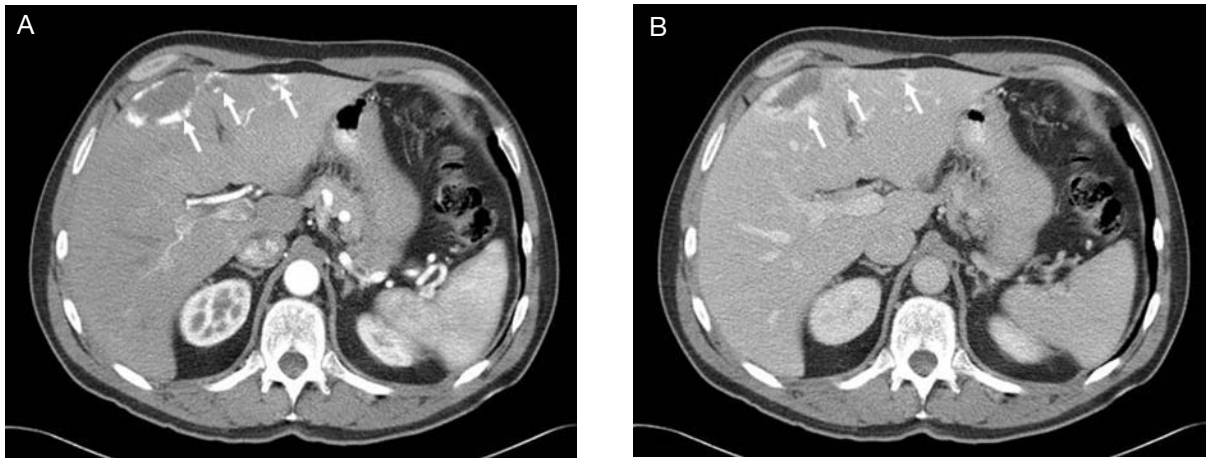


Fig. 3. Cavernous hemangioma. *A*, Peripheral nodular enhancement in the arterial phase (*arrows*, one large and two small cavernous hemangiomas). *B*, Fill-in toward the center of the lesions in the venous phase (*arrows*, contrast enhancement extending toward the center of the masses, with almost complete enhancement of the two small hemangiomas).

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. Hepatic adenoma is associated significantly with long-term use of oral contraceptive pills. The estimated relative risk is 2.5 times greater for women who have taken oral contraceptive pills for 3 to 5 years than for women who have taken them for 1 year or less. After 5 years of oral contraceptive use, the risk sharply increases to 25 times greater after 9 or more years of use. Hepatic adenomas also occur in a familial pattern associated with diabetes mellitus, 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 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 unusual. Recent evidence suggests that adenomas that stain positive for increased cytoplasmic or nuclear β-catenin are more likely to transform to hepatocellular carcinoma.

Histologic Features
Adenomas are characterized by the presence of sheets of hepatocytes without bile ductules, fibrous septa, portal tracts, or central veins.

Clinical Features
Hepatic adenomas are most often asymptomatic. Patients 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 are homogeneous when small. The tumors typically take up contrast rapidly in the arterial phase of contrast CT or MRI studies and then almost immediately become isointense with the surrounding liver in the 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 99m sulfur colloid scintigraphy, there usually is no uptake because adenomas do not contain Kupffer cells. This feature also helps to differentiate adenomas from focal nodular hyperplasias in the delayed phase after MRI with gadobenate dimeglumine, in which adenomas show decreased retention of the contrast when compared with the surrounding liver (Fig. 4).

Biopsy
Because of the frequent uncertainty about the diagnosis after a thorough noninvasive evaluation, biopsy often is required for diagnosis.

Management
Resection is the treatment of choice because of the risk of rupture and associated malignancy. Patients generally are advised to discontinue the use of oral contraceptive pills. 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.

Focal Nodular Hyperplasia
Focal nodular hyperplasia is thought to develop as a reaction of the liver to an intrahepatic arterial

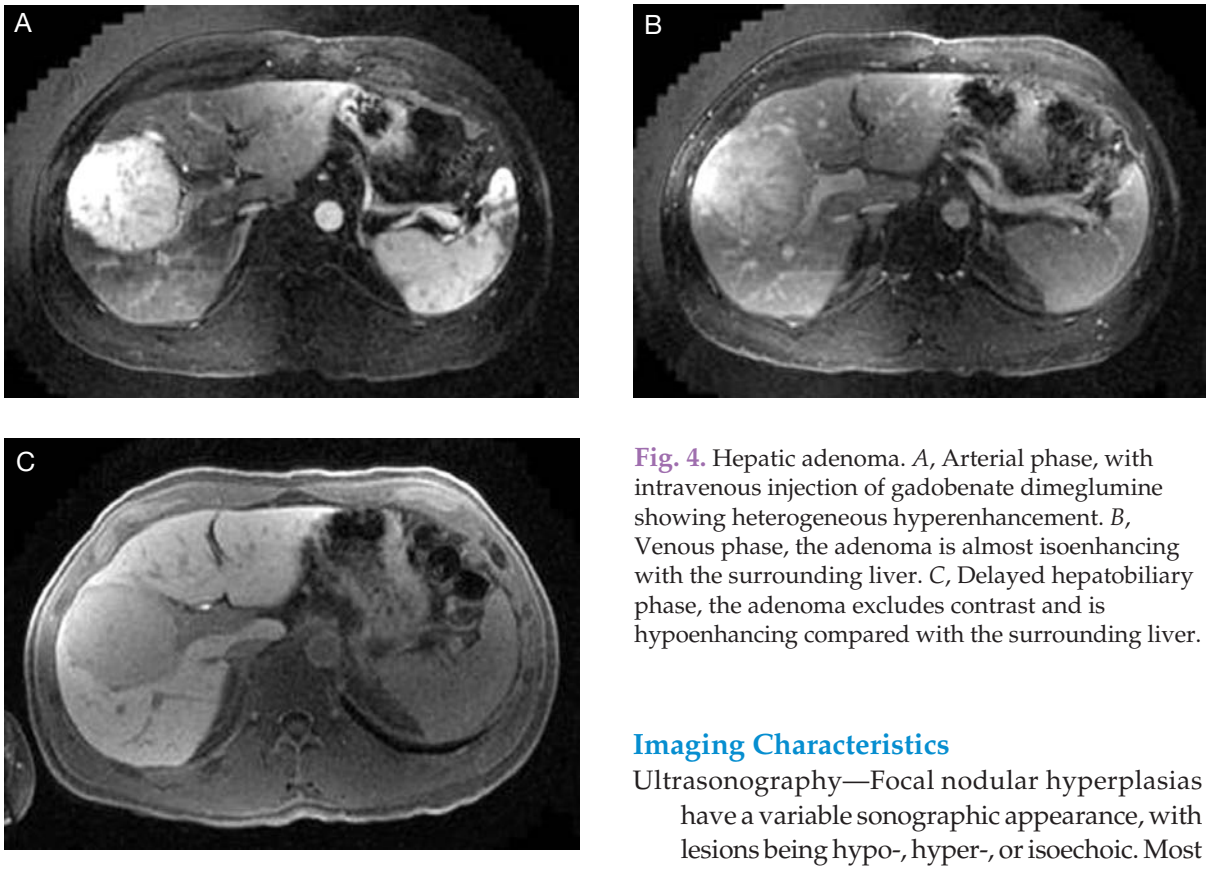


Fig. 4. Hepatic adenoma. *A*, Arterial phase, with intravenous injection of gadobenate dimeglumine showing heterogeneous hyperenhancement. *B*, Venous phase, the adenoma is almost isoenhancing with the surrounding liver. *C*, Delayed hepatobiliary phase, the adenoma excludes contrast and is hypoenhancing compared with the surrounding liver.

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. 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 hyperplasias have a variable sonographic appearance, with lesions being hypo-, hyper-, or isoechoic. Most commonly, the tumors are hypoechoic except for the central scar. A color flow Doppler study may show increased blood flow in the central stellate scar.

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.

MRI with contrast—There is rapid, intense contrast enhancement similar to the pattern with multiphasic CT. Typically, focal nodular hyperplasias are isointense on T1-weighted images and either isointense or slightly hyperintense on T2-weighted images. The central scar is usually hypointense on T1- but hyperintense on T2-weighted images. Gadobenate dimeglumine contrast concentrates in the immature bile ductules and Kupffer cells of the tumor (Fig. 5).

Technetium 99m sulfur colloid scintigraphy—In contrast to the hypointensity of adenomas, 50% to 60% of focal nodular hyperplasias show

hyperintense or isointense uptake because of the presence of Kupffer cells.

Biopsy

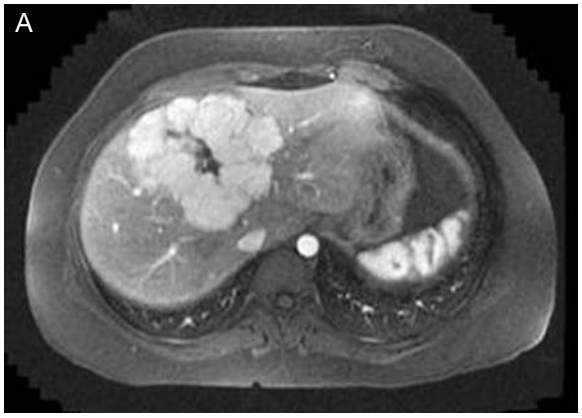
It can be difficult to distinguish between focal nodular hyperplasia and adenoma because fine-needle aspirates from both lesions may show only benign-appearing hepatocytes.

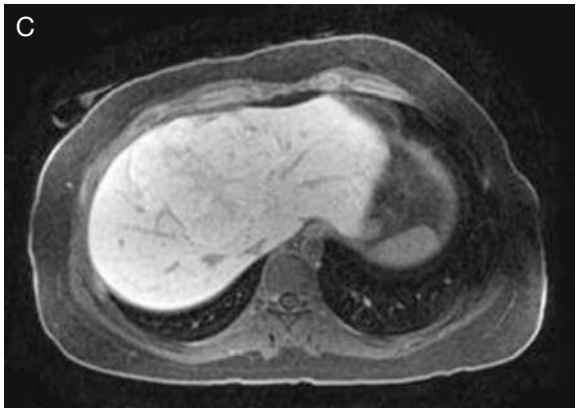
Management

Asymptomatic focal nodular hyperplasias 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, usually asymptomatic, and 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.

Clinical Features

Cysts are usually asymptomatic unless large, when they can cause symptoms through pressure on adjacent structures. Rarely, large cysts may cause biliary obstruction.

Imaging Characteristics

Ultrasonography—This is the best imaging modality for cysts. Classically, cysts are anechoic and have smooth, round margins; a distinct far wall; and posterior acoustic enhancement (Fig. 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.

CT—Cysts have the same density as water and do not change with contrast imaging.

MRI—Cysts are hyperintense on 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.

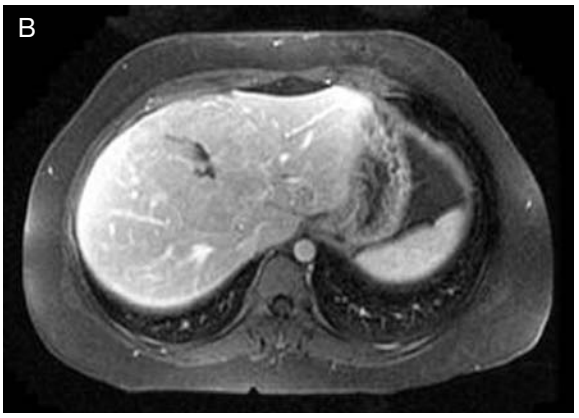


Fig. 5. Focal nodular hyperplasia. *A*, Arterial phase showing homogeneous hyperenhancement and a central scar. *B*, Venous phase, the tumor is isoenhancing with the surrounding liver. *C*, Delayed phase after intravenous injection of gadobenate dimeglumine showing that the contrast concentrates within the tumor.

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.

Histologic Features
Areas of fatty infiltration show fat-laden cells.

Clinical Features
Focal fat or fat sparing is asymptomatic and usually discovered on abdominal imaging performed for other causes.

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.

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.

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.

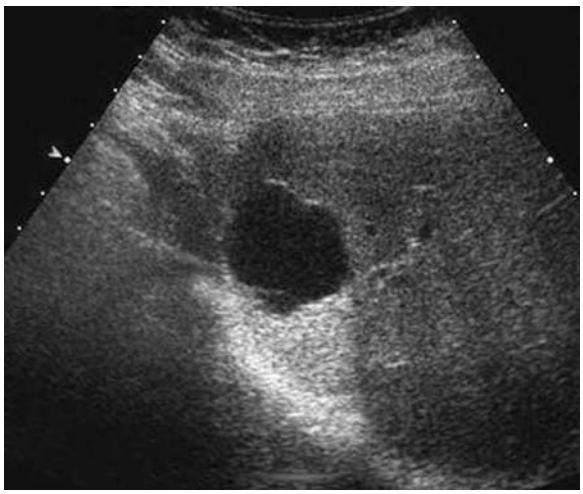


Fig. 6. Simple cyst. Ultrasonogram showing the characteristic changes of absence of echoes within the lesion, a distinct far wall, and increased echogenicity posterior to the cyst.

Biopsy
Biopsy studies can be used to exclude other lesions if the diagnosis cannot be established confidently.

Management
None 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, other causes of liver injury such as α_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 arise in the context of cirrhosis. The other 10% to 20% comprise two groups. The first group includes chronic HBV-infected patients who develop hepatocellular carcinoma in the absence of cirrhosis, presumably due to 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 living in countries with a low incidence of HBV infection who present with sporadic onset 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 the tumor.

Surveillance and Diagnosis With Imaging or Biopsy

The best outcomes for treatment of hepatocellular carcinoma are achieved with liver transplantation, surgical resection, or local ablative therapies such as radiofrequency ablation or percutaneous ethanol injection. Because these therapies are most effective when applied to early-stage hepatocellular carcinoma, there is strong rationale for emphasizing a regular surveillance program to screen for the tumor in at-risk persons. Current guidelines recommend that persons with cirrhosis have 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, 50 years for Asian women, and 50 years for whites. Determining the serum α-fetoprotein level has low sensitivity for the detection of early-stage hepatocellular carcinoma, and its use is not recommended, except when high-quality ultrasonography is not available. The higher basal metabolic index and central obesity of many US patients frequently render full ultrasonographic visualization of the liver difficult; hence, α-fetoprotein measurement remains part of the de facto standard for surveillance of hepatocellular carcinoma.

Once a new mass is identified with ultrasonography, it is confirmed with cross-sectional imaging with contrast 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 (Fig. 7). Hepatocellular carcinoma can be diagnosed noninvasively if a new nodule found during surveillance to arise in a cirrhotic liver shows typical arterial enhancement and venous washout. Current guidelines require that for nodules 1 to 2 cm large, these features be shown by two imaging modalities; for nodules larger than 2 cm, typical features seen on one contrast imaging study are sufficient to establish the diagnosis. The major rationale for noninvasive diagnosis is to prevent tumor seeding and recurrence after immunosuppression in patients who receive a liver transplant. Patients who present with newly discovered liver masses in the absence of cirrhosis and who have not been receiving ongoing surveillance for chronic hepatitis B 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 α-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, can also be associated with a high level of α-fetoprotein.

Management

Liver Transplantation

Liver resection and transplantation offer the greatest chance of cure for patients with hepatocellular carcinoma. The selection of resection versus transplantation is based on a careful evaluation of the comorbid conditions of the patient, liver function, tumor size, number of tumors, vascular invasion, candidacy for transplantation, and organ availability. Transplantation is an effective treatment option for hepatocellular carcinoma of patients with cirrhosis because it addresses both the neoplasm and underlying liver disease. Initially, the outcomes of transplantation for hepatocellular carcinoma were poor, but with advances in patient selection, they have improved substantially. With the current selection criteria of one tumor smaller than 5 cm or up to three tumors smaller than 3 cm, the 5-year survival rate is 70% to 80% and the recurrence rate is less than 15%. Despite the favorable results of transplantation, organ availability is less than the demand and up

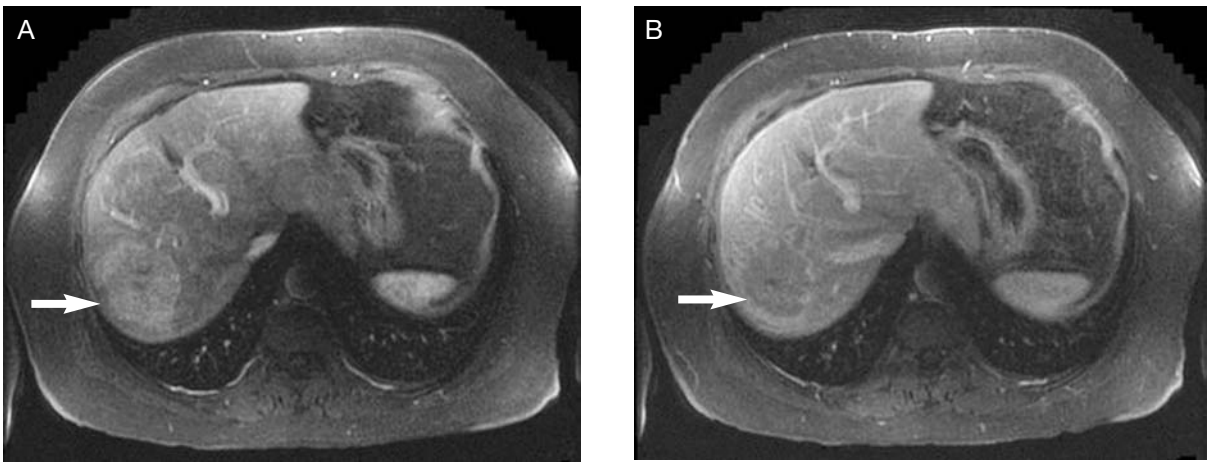


Fig. 7. Hepatocellular carcinoma. *A*, Arterial phase showing vascular enhancement (*arrow*). *B*, Portal phase showing venous washout (*arrow*).

to 15% of patients listed for transplant will drop out because of tumor progression before an organ becomes available.

Surgery

Liver resection is the preferred treatment for 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 can be performed with low mortality rates (<5%), with a 5-year survival rate of 30% to 50%. The major causes of perioperative mortality in patients with cirrhosis who have liver resection are bleeding and liver failure. 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 (single tumor, preserved liver function, absence of portal hypertension), the 5-year survival rate is as high as 50% to 70%.

Local and Locoregional Therapies

Local modalities for treating hepatocellular carcinoma include ablative methods such as percutaneous ethanol injection and radiofrequency ablation (RFA) and locoregional therapies such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and conformal beam radiotherapy.

Percutaneous ethanol injection is performed under ultrasonographic guidance and is used for treatment of small hepatocellular carcinomas up to 3 cm large in patients who are not candidates for liver transplantation or when liver transplantation is not available. Ethanol induces tumor necrosis and is particularly effective in the cirrhotic liver because the surrounding fibrotic tissue limits the diffusion of the injected ethanol. Two or three injection sessions usually are needed for complete ablation of the tumor. The low cost of this treatment makes it attractive for use in lower income countries.

With RFA, a high-frequency electrical current is applied to a treatment probe that is inserted into the tumor. The treatment probes often have multiple small tines that are deployed in a radial fashion within the tumor to increase the size of the

treatment field. The high-frequency current induces temperatures of about 60°C in the tumor tissue, leading to coagulative necrosis. 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 of rapid conduction of heat away from the tumor due to a heat sink effect. 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.

Transarterial chemoembolization (TACE) involves the angiographic injection of a combination of chemotherapy agents with gelfoam 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. 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 benign 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. TACE can be administered to carefully selected patients who have incomplete occlusion of the portal vein. Randomized controlled trials have shown that TACE improves survival of patients with unresectable intermediate-stage hepatocellular carcinoma. The chemotherapy agents typically used for TACE include cisplatin, doxorubicin, and mitomycin C. For TACE, 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.

Transarterial radioembolization (TARE) delivers intratumoral radiation by transarterial injection of yttrium-90 radioactive microspheres, following the principles of TACE. Currently, one product has been approved in the United States for treating hepatocellular carcinoma: TheraSphere (MDS Nordion). TARE has not been studied as rigorously as TACE. Early uncontrolled studies suggest there is a risk of progressive long-term liver decompensation in patients who have more advanced liver disease at the time treatment is initiated.

Systemic Approaches to Therapy

For patients with advanced multifocal disease in the liver or at extrahepatic sites, no safe and effective therapy was available until recently. In early 2007, a large multicenter study showed that the multitargeting kinase inhibitor sorafenib had significant efficacy in a population of mostly Child-Pugh class A patients with unresectable hepatocellular carcinoma, doubling the median time to radiographic progression from 12.3 to 24.0 weeks and increasing overall survival 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.

Cholangiocarcinoma

Cholangiocarcinomas are malignancies that arise from the bile duct epithelium. In Western countries, PSC 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 cytic 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 PSC, the risk of diagnosis of cholangiocarcinoma is highest within the first 2 years after the diagnosis of PSC, suggesting

perhaps that the development of cancer is the event that in some way triggers the diagnosis of PSC. Cholangiocarcinomas are classified as intrahepatic and extrahepatic tumors. The presentation of intrahepatic cholangiocarcinomas is typically as 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 ducts 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 CA19-9. A CA19-9 value more than 100 ng/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 more than 1,000 ng/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 biliary tree (5%-15%). 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, or 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 one lobe of the liver often lead to unilobar biliary obstruction for an extended period, during which time the patient has a normal bilirubin level because of adequate biliary drainage from the unaffected 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* (Fig. 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—Intrahepatic cholangiocarcinomas are hypointense on T1- 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 in 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 via ERCP and percutaneous transhepatic cholangiography (PTC) are becoming less important as initial diagnostic modalities; 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. PTC may be technically challenging in patients with PSC because of peripheral strictures; for these patients, ERCP is the preferred modality. 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.

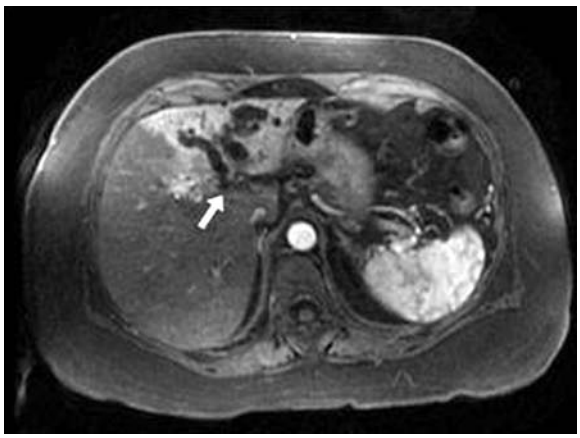


Fig. 8. Cholangiocarcinoma with atrophy-hypertrophy complex. Note cholangiocarcinoma with obstruction of the left biliary ductal system (*arrow*) and consequent marked dilatation of the bile ducts in the left lobe, with associated atrophy of the left lobe parenchyma. The right lobe shows compensatory hypertrophy.

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. Recently, 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 two or more relevant chromosomal loci, typically chromosomes 3, 7, or 17 in the current iteration of the Vysis UroVysion fluorescence in situ probe set that is used, are highly specific for cancer (Fig. 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 has proven 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 Transplantation

A protocol of neoadjuvant chemoradiation followed by liver transplant for patients with hilar cholangiocarcinoma or cholangiocarcinoma arising in association with PSC has been developed at Mayo Clinic Rochester. The protocol is limited to patients who have a mass smaller than 3 cm and excludes patients who have intrahepatic peripheral cholangiocarcinoma, 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 transplantation. Before transplantation, patients undergo a staging abdominal exploration. Regional lymph node metastases, peritoneal metastases, or locally extensive disease preclude transplantation. At the time of the last published review of patients treated since 1993, 71 patients had begun neoadjuvant therapy at Mayo Clinic Rochester and 38 (54%) had had favorable findings at the staging operation and subsequent liver transplantation. The 5-year actuarial survival for all patients that begin neoadjuvant therapy is 58%; the 5-year survival rate for those undergoing transplantation is 82%. These results exceed those achieved with surgical resection even though all the transplant protocol patients have unresectable cholangiocarcinoma or cholangiocarcinoma arising in association with PSC. These results also are comparable to 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,

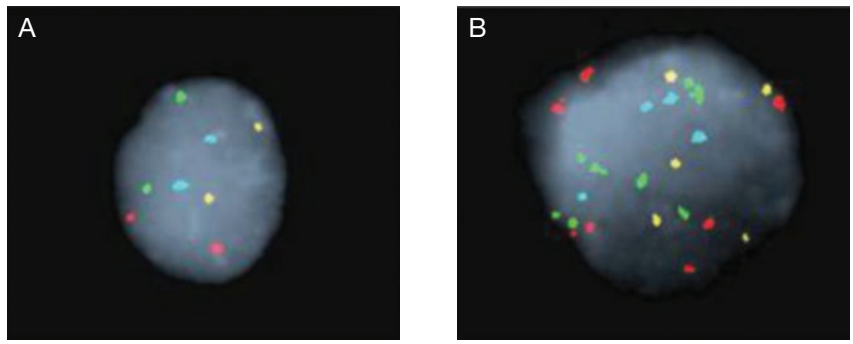


Fig. 9. Fluorescence in situ hybridization for diagnosis of malignancy in biliary strictures. Fluorescent DNA probes for the centromeres of chromosomes 3 (red), 7 (green), 17 (aqua), and the p16 locus at chromosome 9p21 (yellow) are hybridized to brush cytology specimens obtained from biliary strictures at endoscopic retrograde cholangiopancreatography. The normal diploid cell (*A*) has two copies of each of the probes; the malignant polysomic cell (*B*) has multiple copies of chromosomes 3, 7, 9, and 17.

which can be given alone or in combination with either capecitabine or oxaliplatin. These regimens produce responses in 25% to 64% of patients, with a median survival rate of 10 to 15 months. It is not clear whether multiagent therapy has any benefit over 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 (Photofrin) 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 wavelength, is applied endoscopically through a glass fiber inserted to the site of the malignant biliary stricture.

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, 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 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 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.

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CHAPTER 24

Alcoholic Liver Disease

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EPIDEMIOLOGY AND CLINICAL SPECTRUM

Public Health Significance

Alcoholic liver disease is a major cause of morbidity and mortality in the United States. Alcohol is implicated in more than 50% of liver-related deaths in the United States, and complications of alcoholism contribute to a quarter of a million deaths annually. Also, alcoholic liver disease is a major health care cost expenditure, accounting for nearly $3 billion annually.

Clinical Spectrum

The clinical spectrum of alcoholic liver disease includes fatty liver, alcoholic hepatitis, and alcoholic cirrhosis. Fatty liver develops in response to short periods (days) of alcohol abuse. It is generally asymptomatic and reversible with abstinence. More advanced liver injury usually requires prolonged alcohol abuse over a period of years. Of note, the majority of people who abuse alcohol for extended periods do not develop more advanced lesions of alcoholic liver disease. However, approximately 20% of these patients do develop alcoholic hepatitis or alcoholic cirrhosis (or both).

Risk Factors

Alcohol Ingestion

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 equivalent of 6 to 8 drinks per day for several years. In women, half of 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, and clearly factors other than absolute

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model of end-stage liver disease; MEOS, microsomal ethanol oxidizing system; NAD, nicotinamide adenine dinucleotide, oxidized; NADH, nicotinamide adenine dinucleotide, reduced.

ethanol consumption are important in determining which persons develop alcoholic liver disease. A recently identified risk factor is obesity. Other risk factors are described below.

Genetic and Hereditary Factors

The interindividual variability in the correlation between alcohol consumption and development of liver disease highlights 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, most notably mutations in the tumor necrosis factor promoter and in alcohol-metabolizing enzyme systems. 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. Currently, however, no single genetic polymorphism has been shown definitively to contribute to alcoholic liver disease.

Sex

Although alcoholic liver disease is observed more commonly in men than women, women are predisposed to the development of this disease and develop more severe disease with less alcohol consumption than men. The reason for this greater risk in women is not clear; however, despite weight adjustment, 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.

- Alcoholic liver disease encompasses a clinicohistologic spectrum (fatty liver, hepatitis, and cirrhosis).
- Although there is considerable variability among persons, the toxic dose of alcohol necessary for advanced liver injury to develop is probably 60 to 80 g 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.
- 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.
- Alcoholic hepatitis may occur in the presence or absence of preexisting liver cirrhosis.

ETHANOL METABOLISM AND PATHOPHYSIOLOGY

More than one 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) (Fig. 1). The relative importance of each of these pathways is being investigated. 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 (NADH) to the oxidized form (NAD), 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.

MEOS is localized in the endoplasmic reticulum instead of the cytosol, where the alcohol dehydrogenase system operates, and appears to be important in alcohol metabolism when blood levels of alcohol are moderate to high. Under normal conditions when these levels are low, the role of MEOS is much smaller than that of the alcohol dehydrogenase system. As explained by its enzyme kinetics, 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. MEOS also converts alcohol to acetaldehyde, requiring aldehyde dehydrogenase for further metabolism. Importantly, the specific MEOS enzyme CYP2E1 is responsible for the metabolism of various other compounds. The induction of CYP2E1 by alcohol

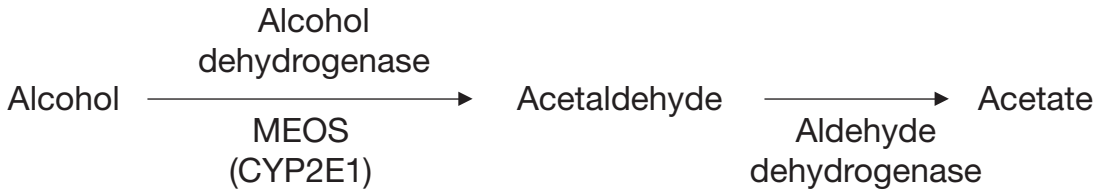

Fig. 1. Alcohol metabolism. Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase and CYP2E1. In most persons, the alcohol dehydrogenase pathway is dominant; however, in alcoholic persons and those with high blood levels of alcohol, CYP2E1 is induced and has a major role in metabolism. Acetaldehyde derived from both these pathways is metabolized by aldehyde dehydrogenase to acetate. MEOS, microsomal ethanol-oxidizing system.

importantly affects blood levels of these compounds and accounts for the increased tolerance of alcoholics to sedatives. Compounds that are rapidly metabolized in alcoholics by this process include isoniazid and acetaminophen. Importantly, nearly one-half of Far East Asians 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, who may also be more susceptible to alcohol-induced liver injury. A similar flushing syndrome is observed in response to alcohol consumption when a person ingests disulfuram, which is the basis for its use in the treatment of alcoholism. Although the peroxisomal catalase enzyme also is capable of ethanol metabolism, its physiologic role in alcohol metabolism appears to be minor.

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, including tumor necrosis factor, a cytokine whose blood levels appear to correlate with the severity of liver disease in patients with alcoholic hepatitis.

- Alcohol dehydrogenase is the primary alcohol-metabolizing pathway, particularly when blood alcohol levels are low.
- MEOS is important in alcoholics, especially when blood levels of alcohol are high. Induction of this system importantly affects the metabolism of various xenobiotics.
- Diminished activity of aldehyde dehydrogenase accounts for the flushing syndrome detected in a large proportion of Asians who consume alcohol.

FATTY LIVER

Case 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 (normal 8-48 U/L), alanine aminotransferase (ALT) 43 U/L (normal 7-55 U/L), γ-glutamyltransferase (GGT) 336 U/L (normal 9-31 U/L); mean corpuscular volume and total bilirubin and alkaline phosphatase levels are normal. On further questioning, the patient admits to having had 6 to 10 drinks per day over the past week during student orientation.

This patient has the clinical features suggestive of alcoholic fatty liver. The diagnosis and treatment are discussed below.

History and Physical Examination

Fatty liver may develop in response to only a transient alcohol insult, over a period of days. The most salient historical feature is an alcohol binge. The patient may be 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. Minor increases in alkaline phosphatase or bilirubin (or both) may be observed. Prothrombin time is 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 (Fig. 2). There are no inflammatory cells or collagen deposition. Because biopsy specimens from patients with Wilson's disease occasionally have the features of steatosis, Wilson's disease should always be excluded in young persons who have abnormal levels of liver 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 entirely reversible. However, 20% to 30% of patients who continue to abuse alcohol chronically develop more advanced forms of alcoholic liver disease, including alcoholic hepatitis and cirrhosis.

- 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 a day 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

Although alcoholic fatty liver is predominantly an asymptomatic condition, a constellation of clinical symptoms, often nonspecific, frequently are observed in patients with more advanced lesions, such as alcoholic hepatitis. Persons 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 lower for women. Also, alcoholic hepatitis may develop in the presence or absence of underlying liver cirrhosis. The clinical presentation of alcoholic hepatitis includes constitutional symptoms such as weakness, anorexia, and weight loss and other nonspecific symptoms such as nausea and vomiting (Fig. 3). Severe alcoholic hepatitis may include more advanced symptoms related to portal hypertension, including gastrointestinal tract 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's disease, and drug-induced hepatitis.

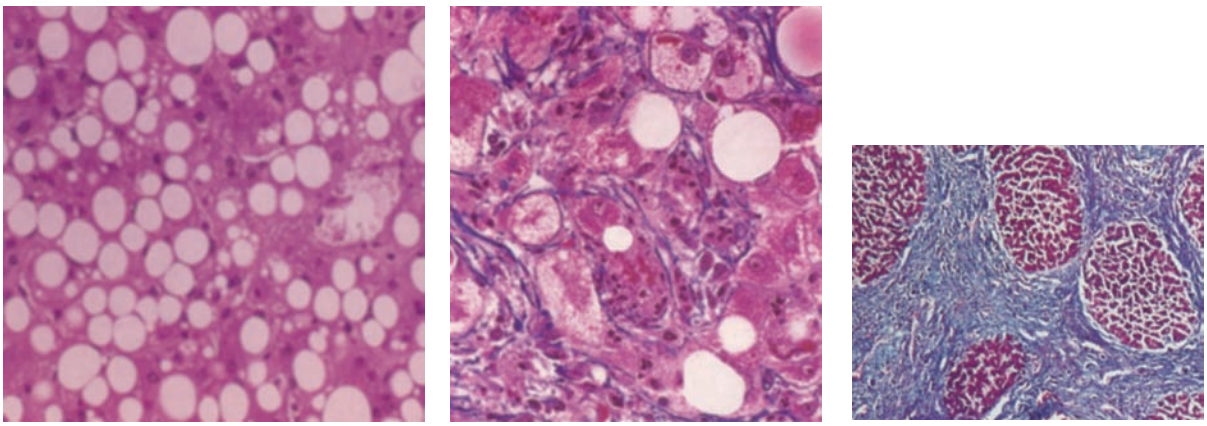

Fig. 2. Histopathologic features of alcoholic liver disease. *A*, Fatty liver. Note macrovesicular steatosis and lack of inflammation and collagen deposition. *B*, Alcoholic hepatitis. Note polymorphonuclear infiltrates, hepatocyte necrosis, steatosis, Mallory bodies, and variable amounts of fibrosis. *C*, Alcoholic cirrhosis. Note characteristic micronodular cirrhosis, although a mixed nodularity pattern is often observed. Frequently, there is prominent secondary hemosiderosis. (From Kanel GC, Korula J. Liver biopsy evaluation: histologic diagnosis and clinical correlations. Philadelphia: WB Saunders Company; 2000. p. 39, 89, 94. Used with permission.)

The diagnosis of alcoholic hepatitis is contingent on determining whether the patient is abusing alcohol. This is not always easy because alcoholic persons and even 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 because of the type of relation between the patient and caregiver and the approach and persistence of different history takers. 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* back on alcohol use? Has the patient become *annoyed* with other persons' concerns about his or her alcohol use? Does the patient feel *guilty* about his or her alcohol use? Does the patient use alcohol in the morning as an *eye*-opener? Although two 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 of alcohol abuse.

In patients with alcoholic hepatitis, physical examination findings are most notable for tender hepatomegaly, fever, and tachycardia (Fig. 3). 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. Evidence for concomitant infection is common and may be detected on examination, including signs of spontaneous bacterial peritonitis, pneumonia, or cellulitis.

Laboratory and Radiographic Features

Laboratory abnormalities reflect the extrahepatic adverse effects of alcohol as well as alcohol-induced liver injury (Table 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 leukemoid reaction also may be observed. Aminotransferase levels usually are increased less than 5 to 10 times normal, but they may be higher with concomitant acetaminophen toxicity. Also,

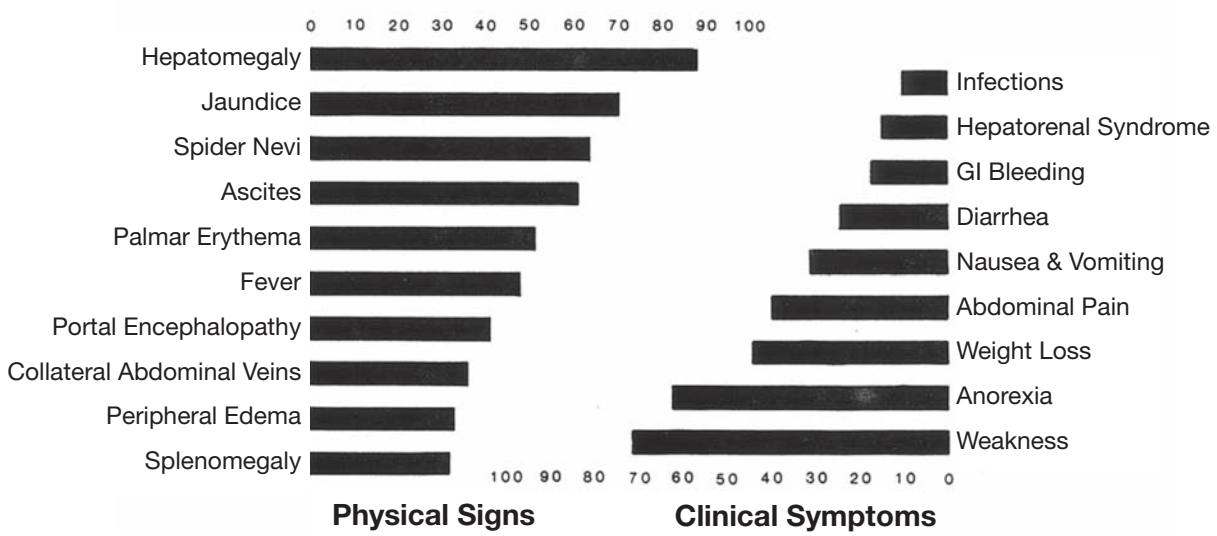

Fig. 3. Clinical features of alcoholic hepatitis. Clinical symptoms of alcoholic hepatitis are often nonspecific and include weakness, anorexia, and abdominal pain. In more severe cases, complications of portal hypertension predominate, including gastrointestinal (GI) tract bleeding and renal dysfunction. Physical examination findings are most notable for hepatomegaly and jaundice. Additional findings depend on the presence of portal hypertension or liver cirrhosis (or both), including stigmata of chronic liver disease and collateral vessels. Numbers refer to percentage of patients with the feature. (From Mendenhall CL. Alcoholic hepatitis. In: Schiff L, Schiff ER, editors. Diseases of the Liver. Vol 2. 7th ed. Philadelphia: JB Lippincott Company; 1993. p. 862. Used with permission.)

the level of AST almost always is higher than that of ALT, which is opposite to that in nonalcoholic steatohepatitis, in which the ALT level is often higher than the AST level. Both the modest increase in aminotransferase levels and the greater increase in AST than in ALT help to differentiate alcoholic hepatitis from alternative diagnoses. Some laboratory abnormalities reflect the severity of the alcohol-induced liver injury and are prognostically useful, including prothrombin time and bilirubin concentration. In moderate to severe cases of alcoholic hepatitis, prothrombin time and bilirubin concentration are increased, and, in contrast to aminotransferase levels, prothrombin time and bilirubin concentration have prognostic utility. Several groups have attempted to use bilirubin concentration and prothrombin time as well as other laboratory variables to assess the prognosis of patients with alcoholic hepatitis. The most widely used of these assessments is the Maddrey discriminant function analysis:

Discriminant function = 4.6 (prothrombin time – control) + serum bilirubin concentration (mg/dL)

A discriminant function greater than 32 effectively identifies patients whose risk of death is higher than 50%. The model of end-stage liver disease (MELD) score also predicts survival in patients with alcoholic hepatitis. MELD score and corresponding 90-day survival can be calculated on the basis of the patient's creatinine, international normalized ratio (INR), and bilirubin values at the following Web site: http://www.mayoclinic.org /girst/mayomodel7.html. 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

Table 1. Laboratory Abnormalities in Alcoholic Hepatitis

Hematology
Macrocytic anemia (increased MCV)
Leukocytosis
Thrombocytopenia
General chemistry
Hyperglycemia
Hyperuricemia
Hypertriglyceridemia
Ketosis
Tests of liver function and injury
Hypoalbuminemia
Hyperbilirubinemia
Increased prothrombin time
Increased AST/ALT (ratio of 1.5 to 2.5 and total increase <10-fold)
Increased GGT
Increased alkaline phosphatase (mild)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; MCV, mean corpuscular volume.

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.

Because of the inherent difficulties in obtaining a reliable history of alcohol use, various biochemical markers have been evaluated for the detection of surreptitious alcohol abuse. Many of the traditional serologic tests of alcohol abuse are based on indirectly assessing alcohol abuse by examining such markers of liver injury as AST, ALT, the ratio of AST to ALT, 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 bone marrow toxicity of alcohol; it can be helpful as an adjunctive test. Newer tests include carbohydrate-deficient transferrin and mitochondrial AST. Carbohydrate-deficient transferrin reflects the desialylation of transferrin that occurs 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-to-ALT ratio, GGT, and mean corpuscular volume.

Histologic Features

With advances in noninvasive liver diagnostic capabilities over the past decade, the diagnosis of alcoholic hepatitis often is 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's 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 with HCV antibody positivity. Liver biopsy, if pursued, often requires a transjugular rather than a percutaneous route, depending on the degree of coagulopathy and thrombocytopenia. In alcoholic hepatitis, liver biopsy specimens demonstrate several characteristic features, including centrilobular and sometimes periportal polymorphonuclear infiltrates, centrilobular hepatocyte swelling, ballooning degeneration, macrovesicular steatosis, and Mallory bodies (Fig. 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 an 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) 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%.

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 30 to 40 kcal/kg ideal body weight of caloric supplementation and 1 to 1.5 g protein/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 should not require protein restriction in most patients. For patients with severe encephalopathy that is exacerbated by dietary protein, branched chain amino acid supplements should be considered or protein intake should be decreased transiently. Increased use of dietary vegetable protein may be better tolerated than animal protein. Other than for this scenario, amino acid supplementation probably does not improve survival sufficiently for the added cost.

Portal Hypertension

Patients with alcoholic hepatitis may develop complications of portal hypertension regardless of the presence or absence of underlying cirrhosis. This clinical observation is supported by studies demonstrating 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.

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.

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 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 had a survival benefit for patients with a discriminant function greater than 32 or hepatic encephalopathy (or both). Currently, the use of corticosteroid therapy for alcoholic hepatitis varies among experienced hepatologists.

Other Treatment Options

Alcohol induces oxidative stress in the liver, resulting in an imbalance between oxidants and antioxidants. To decrease oxygen consumption by

the liver, investigators have studied the role of propylthiouracil in treating alcoholic hepatitis. Although a randomized controlled trial showed clinical benefit, the results of follow-up studies have been inconclusive. Also, because of the inherent hepatotoxicity of propylthiouracil, this drug remains experimental. Another putative antifibrotic agent, colchicine, has been evaluated in treating alcoholic hepatitis. Although an initial trial suggested that the drug was beneficial for treating alcoholic liver cirrhosis, no clinical benefit has been demonstrated for hepatitis. Other hepatoprotective compounds, such as *S*-adenosyl-L-methionine and phosphatidylcholine, may have a small beneficial effect but are not widely used outside of research protocols. The results of a recent study have suggested that pentoxifylline, an inhibitor of tumor necrosis factor, is of clinical benefit. Because the toxicity profile of pentoxifylline is low, its use for alcoholic hepatitis is prevalent; however, confirmatory studies are needed. Ongoing clinical studies are focusing on several different anticytokine and antioxidant therapies.

- Liver biopsy should be considered if the cause of hepatitis is questioned and specific treatments for alcoholic hepatitis other than supportive care 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 aminotransferase (ALT and AST) increase.
- 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 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

For persons with a clinical history of marked and prolonged alcohol abuse, only about 20% eventually develop liver cirrhosis. The presence or absence of symptoms is due largely to the presence or absence of liver decompensation. Patients with cirrhosis and compensated liver function who are abstinent 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 may demonstrate stigmata of chronic liver disease (spider angiomas and palmar erythema), complications of portal hypertension (ascites, splenomegaly, asterixis, and pedal edema), excess estrogen (gynecomastia and hypogonadism), and systemic alcohol toxicity (peripheral neuropathy, dementia, and Dupuytren's 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-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 and colloid shift to spleen and bone marrow on liver and spleen scanning. Dynamic triple-phase computed tomography may show changes in liver contour, splenomegaly, collateralization, or ascites. Patients are at risk for

hepatocellular carcinoma and should be evaluated biannually with ultrasonography and the serum α-fetoprotein test, particularly patients who have had recent clinical decompensation.

Histologic Features

Traditionally, alcoholic cirrhosis is classified as a micronodular cirrhosis (Fig. 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 aforementioned histologic features of alcoholic hepatitis also are present. Patients are at risk for hepatocellular carcinoma, particularly those with coexisting chronic viral hepatitis.

Prognosis and Treatment

A good prognosis depends on the absence of liver decompensation and complications of portal hypertension and the ability to maintain abstinence. The prognosis for patients with cirrhosis who are well compensated and able to maintain abstinence is reasonably good, with a 5-year survival rate greater than 80%. Even for patients with decompensation, the 5-year survival rate with abstinence is greater than 50%. However, patients who continue to drink have a much worse prognosis, with a 5-year survival rate less than 30%.

The only established effective treatment for alcoholic cirrhosis is liver transplantation. Currently, alcoholic liver disease is the second most common indication for liver transplantation in adults in the United States. However, fewer than 20% of patients with end-stage alcoholic liver disease have transplantation. Despite perceptions to the contrary, patients who have liver transplantation for alcoholic liver disease have survival rates after transplantation comparable to those of patients who have transplantation for other indications. Indeed, the risk of cellular rejection is lower for persons undergoing transplantation for alcoholic liver disease than for those with other conditions.

A major issue in maintaining excellent outcome for this population focuses on identifying candidates with a low risk of recidivism after transplantation. Alcohol relapse after transplantation varies among centers and is difficult to quantify accurately, but it is probably about 15% to 30%. Although detecting surreptitious alcohol use after transplantation is often difficult, the low incidence of graft loss from recurrent alcoholic liver disease suggests that most patients who return to drinking after transplantation do not drink to the point of damaging the graft. However, it must be considered that alcohol abuse after liver transplantation can cause rapid development of cirrhosis in the graft, interfere with compliance in taking immunosuppressive medications, and alter the perception of the general public of liver transplantation, thus adversely affecting potential organ donors. Therefore, selecting patients who are appropriate for liver transplantation requires a team involving a hepatologist, surgeon, addiction specialist, psychiatrist, and social worker. Currently, many transplant centers require 6 months of abstinence and appropriate addiction treatment before performing a liver transplant. Appropriate family and social support is also important. Generally, patients with active alcoholic hepatitis are not candidates for liver transplantation because they have not been abstinent for 6 months and they have high perioperative mortality. Also, many of these patients will have evidence of marked clinical improvement after 6 months of abstinence, thereby delaying or obviating liver transplantation.

- Alcohol is a cause of micronodular cirrhosis, but often mixed micro-macronodular cirrhosis is observed histologically.
- The only curative treatment for alcoholic cirrhosis is liver transplantation; however, only a small proportion of patients undergo transplantation, partly because of their inability to maintain prolonged abstinence.
- Transplantation outcomes for alcoholic liver disease are comparable to those for most other indications.

SPECIAL CLINICAL SITUATIONS

Alcohol and Hepatitis C

The increase in prevalence of HCV infection among alcoholic persons is 10 times that of 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 only HCV infection. 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. 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 is unclear. Patients with alcoholic liver disease who have concomitant viral hepatitis have a risk almost fivefold 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 be advised against alcohol use.

Alcohol and Acetaminophen

Alcoholic persons are at increased risk for acetaminophen-induced hepatotoxicity. As little as 2.5 to 3 g per day of acetaminophen may result in pronounced toxicity. The reason for this is that both alcohol and acetaminophen are metabolized in part by cytochrome P-450 2E1, an enzyme in 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*-benzoquinoneimine, 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 alcoholic persons. Thus, in this population, the clinical presentation of acetaminophen toxicity is distinct from that of alcoholic hepatitis. Aminotransferase levels are markedly increased, often more than 1,000 U/L, which is distinctly unusual for alcoholic hepatitis.

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CHAPTER 25

Vascular Diseases of the Liver

Patrick S. Kamath, MD

Vascular diseases of the liver can be divided into disorders of hepatic inflow (ie, diseases of the portal venous and hepatic arterial inflow) and disorders of hepatic venous outflow (Table 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 mid rectum and includes the spleen, 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. For most of its course, this artery lies in the mesentery, with the ileocolic artery being the terminal branch. The superior mesenteric artery gives off three sets of branches: 1) several small branches to the pancreas and duodenum before entering the mesentery, 2) three 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.

Table 1. Vascular Diseases of the Liver

Disorders of portal venous inflow
Acute mesenteric/portal venous thrombosis
Chronic mesenteric/portal venous thrombosis
Disorders of hepatic arterial inflow
Hepatic artery thrombosis
Hepatic arteriovenous fistula
Ischemic hepatitis
Disorders of hepatic venous outflow
Veno-occlusive disease
Budd-Chiari syndrome

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; TIPS, transjugular intrahepatic portosystemic shunt.

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 two 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 supplies 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 drainage of blood, 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."

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. The latter, 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 for sinistral portal hypertension is not warranted.

Patients with isolated chronic mesenteric venous thrombosis often remain asymptomatic because of extensive collateral venous drainage. Occasionally, some patients have gastrointestinal tract hemorrhage, and the use of pharmacologic agents such as propranolol is recommended to prevent variceal bleeding. Endoscopic therapy is used both to control active bleeding and to prevent rebleeding. Surgical intervention, such as 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 may be considered, such as anastomosing a large collateral vein with a systemic vein. Also, gastroesophageal devascularization may be considered. For patients with thrombophilia, anticoagulation may be initiated after the risk of bleeding has been decreased with surgical stents.

DISORDERS OF HEPATIC ARTERIAL INFLOW

Hepatic Artery Thrombosis

Aside from patients who have had liver transplantation, the prevalence of hepatic artery thrombosis is not certain. Hepatic artery thrombosis is the cause of considerable morbidity and mortality in approximately 7% of adults and in perhaps as

many as 40% of pediatric patients undergoing orthotopic liver transplantation. The problem is more extensive in the pediatric age group because of the small 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 technical aspects of the arterial anastomosis being the most important risk of 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. The acute presentation, or 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 the time point between early and late hepatic artery thrombosis. However, the later that hepatic artery thrombosis develops after liver transplantation, 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, 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 visceral angiography may be necessary to confirm the diagnosis. When hepatic artery thrombosis is detected early after liver transplantation, surgical correction usually is recommended.

Hepatic Artery Aneurysm

Although aneurysm of the hepatic artery (Fig. 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 such as 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 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.

Ruptured hepatic artery aneurysms are associated with a high mortality rate because, for most patients, the diagnosis is made only after rupture. The treatment for 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 less 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 and reconstruction of the aneurysm. Intrahepatic aneurysms may be treated also with liver resection.

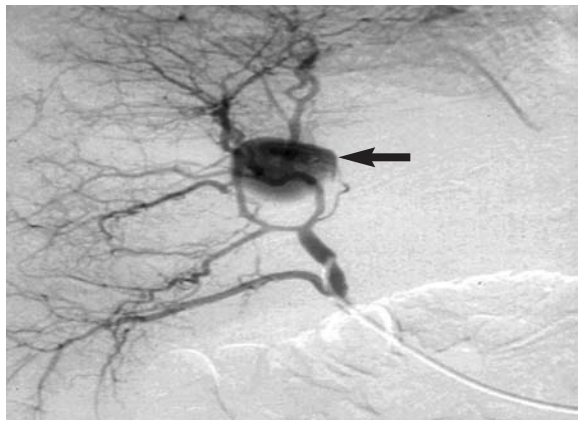

Fig. 1. Selective hepatic angiogram showing an aneurysm (*arrow*) of the intrahepatic portion of the hepatic artery.

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. If untreated, a fistula may result in cardiac failure. The best treatment is embolization and occlusion of the fistula. The usual result is complete cure of the portal hypertension.

Ischemic Hepatitis

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, resulting in ischemic necrosis of the liver. Typical manifestations of ischemic hepatitis are a rapid increase over 24 to 48 hours in the serum level of aminotransferases (aspartate aminotransferase and alanine aminotransferase), to several thousand units, sometimes more than 10,000 U/L. This value rapidly returns 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 hepatitis may result in fulminant liver failure.

Other causes of ischemic hepatitis are hypovolemic shock of any cause and obstructive sleep apnea. Postoperative patients particularly 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 in 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 fistulae 1) between the hepatic artery and hepatic vein (the most common abnormality), 2) between the hepatic artery and portal vein, or 3) between the portal vein and hepatic vein (or a combination of these three). Previously, the most common liver disease in patients with HHT was transfusion-related hepatitis, but currently the most common manifestation is high-output cardiac failure as a result of hepatic artery-to-hepatic vein fistulae. Additional abnormalities include recurrent cholangitis due to the diversion of hepatic arterial blood, either to the hepatic vein or portal vein; portal hypertension as a result of hepatic artery-to-portal vein fistulae, or nodular regenerative hyperplasia; and hepatic encephalopathy because of fistulae between the portal vein and hepatic vein. Embolization of these fistulae is not recommended because of the high risk of liver abscesses. This likely is related to most patients having some degree of portal vein-to-hepatic vein fistula, and once the hepatic artery is occluded, there is neither hepatic arterial nor portal venous blood to the involved segment of the liver. Liver transplantation has been performed to treat HHT and is best indicated for patients who have recurrent cholangitis.

DISORDERS OF HEPATIC VENOUS OUTFLOW

Veno-occlusive Disease

Veno-occlusive disease, or sinusoidal obstruction syndrome, results from occlusion of the central and sublobular hepatic veins. In the United States, the most common cause of veno-occlusive disease is preconditioning for bone marrow transplantation. 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 on veno-occlusive disease of the liver in relation to patients undergoing bone marrow transplantation. For these patients, the incidence of veno-occlusive disease is approximately 50%, with a mortality rate of 20% to 40%. Early changes are related to hemorrhage in zone 3, as seen in liver biopsy specimens. Diagnostic criteria include subendothelial thickening of at least one terminal hepatic venule in association with luminal narrowing.

The pathogenesis of veno-occlusive 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.

Clinical criteria for diagnosing veno-occlusive disease are either the Seattle or the Baltimore criteria. The Baltimore criteria reflect more severe veno-occlusive disease and require a weight gain of more than 5% in association with hepatomegaly and ascites. The Seattle criteria require a bilirubin level greater than 2 mg/dL in association with hepatomegaly, right upper quadrant pain, and a weight gain of more than 2%. According to both the Baltimore and Seattle criteria, the criteria should be met within 3 weeks after bone marrow transplantation. Bilirubin levels greater than 15 mg/dL are associated with poor outcome.

Treatment of veno-occlusive 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 veno-occlusive disease also is debated. Tissue plasminogen activator and heparin have been administered to patients at high risk for dying of complications of veno-occlusive disease. If there is no response to thrombolytic therapy, either a surgical shunt or 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 veno-occlusive 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 veno-occlusive 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 causes predisposing to 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 are detected in up to 87.5% of patients with Budd-Chiari syndrome, particularly myeloproliferative disorders. 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 in patients with 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 and venous thrombosis, but the correlation between protein C and protein S levels and the risk of thrombosis is not precise. In several patients with Budd-Chiari

syndrome, protein C deficiency has been associated also 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 hepatic vein occlusion and whether collateral circulation has developed to decompress the liver. Vague 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 one or two 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 in patients with suspected Budd-Chiari syndrome. It demonstrates the hepatic veins, splenic vein, portal vein, and inferior vena cava. Necrotic areas 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 in a patient with a fulminant or acute presentation, contrast venography may be necessary if radiologic imaging is not diagnostic. The characteristic appearance of the hepatic veins in Budd-Chiari syndrome is that of a spider's web 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 work-up should be performed to exclude the various disorders outlined in Table 2, including demonstrating *JAK2* mutations to determine if the patient has a myeloproliferative disorder.

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 transplantation (Table 3). 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 of 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.

Table 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's syndrome
    - Inferior vena cava webs
    - Trauma
    - Inflammatory bowel disease
    - Dacarbazine therapy
  - Idiopathic

From Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. N Engl J Med. 2004;350:578-85. Used with permission.

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 to reverse hepatic necrosis and to prevent chronic sequelae of hepatic venous outflow obstruction. 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 transplantation 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 3. 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 transplantation in fulminant BCS Acute BCS Subacute BCS if portacaval pressure gradient <10 mm Hg or occluded IVC	Low mortality Useful even with compression of IVC by caudate lobe	High rate of shunt stenosis Extended stents may interfere with liver transplantation
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
Liver transplantation	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

IVC, inferior vena cava; TIPS, transjugular intrahepatic portosystemic shunt.
From Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. N Engl J Med. 2004;350:578-85. Used with permission.

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CHAPTER 26

Portal Hypertension-Related Bleeding

Patrick S. Kamath, MD

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). Primary prophylaxis is pharmacologic therapy with β-blockers or variceal band ligation if β-blocker therapy fails or the therapy is not tolerated by the patient. Active bleeding is best treated endoscopically. Either pharmacologic or endoscopic therapy is appropriate for secondary prophylaxis. Surgical shunts or transjugular intrahepatic portosystemic shunts (TIPSs) are second-line therapy.

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.

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 vasodilation. The hyperdynamic circulation is characterized in the splanchnic circulation by vasodilation 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 gastric and intestinal vascular ectasia, esophageal and gastric varices and portal hypertensive gastropathy occur in patients who have portal hypertension.

Abbreviation: TIPS, transjugular intrahepatic portosystemic shunt.

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 and defective coagulation, portal pressure, and the size of the rent in the varix. Endoscopic sclerotherapy or band ligation attempts to decrease flow through the varix by inducing thrombosis and, ultimately, obliteration of varices.

Therapy

The current recommendations for treatment are summarized in Table 1.

Primary Prophylaxis

All patients with cirrhosis should have endoscopy to screen for the presence and size of esophageal varices. In approximately 25% of patients, varices bleed, usually within the ensuing 2 years. For patients with large varices and advanced liver disease, the risk of hemorrhage can be as high as 75%. Thus, prophylactic therapy is indicated for patients with large varices (>5 mm in diameter). The presence or absence of high-risk endoscopic signs such as red wales does not influence the decision to initiate therapy. Prophylactic treatment may be considered also for patients with Child-Pugh class C status and small varices. If no varices are detected at endoscopy, the procedure should be repeated in 2 or 3 years.

The established primary prophylaxis is treatment with nonselective β-adrenergic blocking agents (β-blockers) such as propranolol and nadolol or with endoscopic variceal ligation. It is important to use only nonselective agents rather than β_1-selective agents. 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/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. 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. Nitrates have no place in primary prophylaxis, either when administered as single agents or in combination with β-blockers.

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 side 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 efficacy or mortality risk between the two treatments. Thus, 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 with 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

Table 1. Recommendations for Treatment of Esophageal Variceal Bleeding

	First-line therapy	Second-line therapy	Other
Primary prophylaxis	β-Blockers or endoscopic variceal ligation		
Control of bleeding	Endoscopy + pharmacologic treatment	TIPS	
Secondary prophylaxis	Endoscopy + β-blockers	TIPS	Liver transplantation

TIPS, transjugular intrahepatic portosystemic shunt.

is seldom used. Nitroglycerin is used in conjunction with vasopressin to further decrease portal pressure and reduce the ischemic side 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 μg, followed by an infusion at 50 μg/hour for 5 days in conjunction with endoscopic variceal band ligation.

For treating active bleeding, the use of surgical shunts and TIPS is limited to patients with refractory bleeding or immediate rebleeding after two separate unsuccessful attempts at endoscopic intervention performed within 24 hours. Frequently, TIPS is preferred to surgical intervention, particularly in patients with Child-Pugh class B or C status. Also, gastric varices can be obliterated concomitantly with TIPS through the injection of gel foam or coils into the gastroesophageal collateral vessels. A surgical shunt should be considered for patients with Child-Pugh class A status and patients for whom continued medical surveillance will be unlikely, because TIPS requires close ultrasonographic follow-up of the shunt to evaluate for restenosis. The type of surgical shunt used depends on institutional expertise and the patient's potential as a candidate for liver transplantation.

Supportive and resuscitative care includes airway protection, volume replacement, treatment of coagulopathy, and vigorous surveillance and treatment of concomitant infection. Maintenance of a hematocrit of 25% to 30% is appropriate because aggressive transfusion of blood products may precipitate further bleeding by increasing portal pressure. Antibiotic prophylaxis for 7 days with norfloxacin 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 prevent and treat hepatic encephalopathy.

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, either alone or in combination with oral nitrates, endoscopic sclerotherapy or 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 or 4 weeks. Varices usually can be obliterated over several weekly sessions. Combination therapy of band ligation and β-blockers may be preferable 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 transplantation. 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. Surgical shunts are recommended for patients with excellent liver synthetic function who are unlikely to require liver transplantation in the near future. All appropriate patients who have variceal hemorrhage should be evaluated for liver transplantation.

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 empiric approach.

Gastric Varices

The most common type of gastric varices is esophageal varices that extend into the cardia of the stomach and are readily treated with endoscopic techniques such as sclerotherapy or band ligation. Varices in the fundus of the stomach, either as an extension of esophageal varices or as isolated gastric fundal varices, are the most common source of gastric variceal bleeding. 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 as determined by 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 with injection of cyanoacrylate glue. Currently, however, this is not readily available in the United States. Other options include sclerotherapy with ethanolamine oleate or thrombin, but the success rate has varied. Gastric variceal ligation should be limited to varices in the cardia.

Although pharmacologic therapy, for example, β-blockers, may be used to prevent gastric variceal rebleeding, no studies support this practice. Our policy 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 reserved 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 more 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, in patients with advanced stages of liver disease as noted by the Child-Pugh

classification, in patients with esophageal varices, and in patients who previously have had esophageal variceal therapy. These lesions also are more common in patients with gastric varices. Approximately 3% of patients with 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 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 transplantation. 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 (Fig. 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 transplantation.

Treatment of gastric vascular ectasia is difficult. Some patients may be managed only with 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 or laser therapy, may be tried, but the results, especially in the diffuse form, are poor. 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 may respond to estrogen-progesterone combinations. We typically prescribe a combination of mestranol, 50 mg, with norethindrone, 1 mg daily, for these patients.

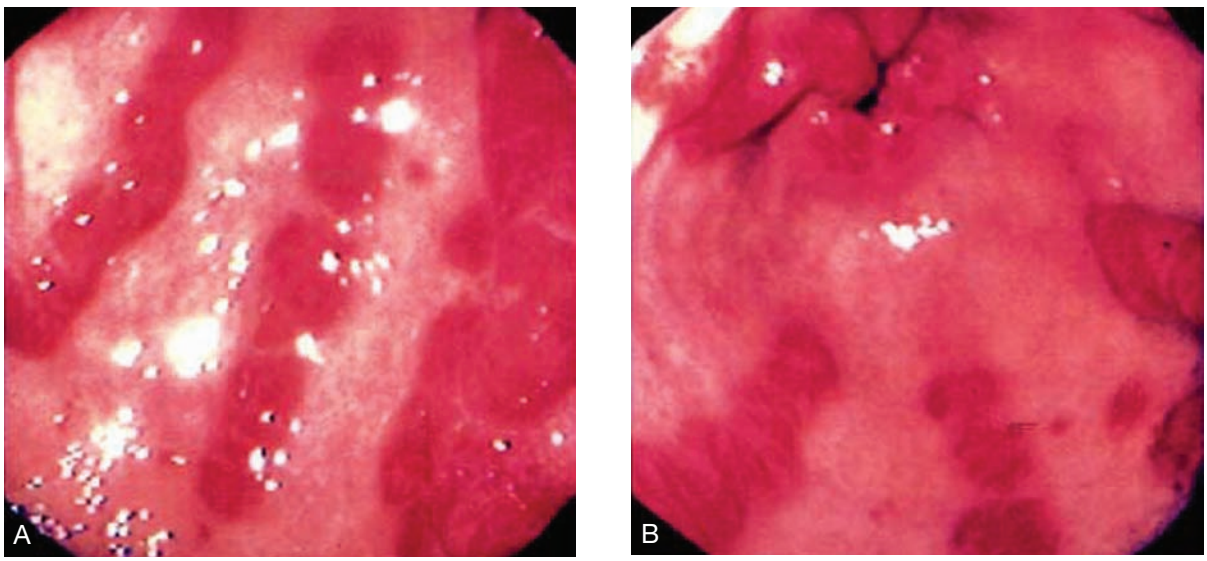

Fig. 1. *A* and *B*, Gastric antral vascular ectasia. Note the linear aggregates of red markings in the antrum and the absence of an underlying mosaic-like pattern.

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CHAPTER 27

Ascites, Hepatorenal Syndrome, and Encephalopathy

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The portal hypertension and hepatic synthetic dysfunction of cirrhosis cause three main complications as liver disease progresses: variceal bleeding, ascites, and hepatic encephalopathy.

ASCITES

Ascites is the most common major complication 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 a median survival of 2 to 5 years.

Pathogenesis of Ascites

The hemodynamic changes in chronic liver disease and portal hypertension are much better understood now and have led to 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) vasodilation, 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). 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

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; PSE, portosystemic encephalopathy; SAAG, serum-ascites albumin gradient; TIPS, transjugular intrahepatic portosystemic shunt.

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 hepatocytes and endothelial membranes, the oncotic pressure gradient within the sinusoids is very low and unable to 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 portal 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 (Table 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, 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. In all cases, ascitic fluid analysis should include a cell count, both total nucleated and 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 greater than 1.1 g/dL confirms, with more 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 this case the total protein concentration in the ascites is usually more than 2.5 g/dL (the value is <2.5 g/dL in cirrhosis-related portal hypertension) (Table 2).

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, for example, lactate and pH, generally have been found to offer little or no additional information. Gram staining is rarely ever positive.

Table 1. Diagnostic and Therapeutic Algorithm for Patients With Ascites

- Does the patient have cirrhosis?
- If yes, are there any other complicaitons of cirrhosis—spontaneous bacterial peritonitis, portal vein thrombosis, active liver disease, malignancy
- Prognostic factors for therapy—urinary sodium excretion, renal function
- Consideraton of therapeutic options

Table 2. Ascitic Protein and Serum-Ascites Albumin Gradient (SAAG)

	SAAG, g/dL	
	≥1.1	<1.1
Total protein, g/dL		
<2.5	Cirrhosis Acute liver failure	Nephrotic syndrome Myxedema
≥2.5	Congestive heart failure Constrictive pericarditis Budd-Chiari syndrome Venoocclusive disease	Peritoneal carcinomatosis Tuberculous peritonitis Pancreatic ascites 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 by performing liver tests or imaging studies. Renal function and renal sodium excretion should be assessed because they are clinical predictors of a therapeutic response: patients with normal blood 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 of 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, sequentially by a low sodium diet and then by diuretics. Only about 10% of patients with cirrhotic ascites have a response to salt restriction alone (with or without bed rest). With the initiation of spironolactone therapy, the ascites will be controlled in 65% of patients 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/day (88 mEq), and then diuretic therapy. Spironolactone, an aldosterone antagonist, is an effective diuretic in most patients with nonazotemic cirrhosis with ascites and is more effective than furosemide for single-agent therapy. Spironolactone is given at an initial dose of 100 mg/day, with 100-mg/day increments as appropriate to 400 mg/day, according to the clinical response and side effects, particularly hyperkalemia. Furosemide is usually started at a dose of 40 mg/day in combination with spironolactone and increased in 40-mg/day increments to 160 mg/day until the desired effect is achieved or side 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. Generally, a weight loss of 0.5 to 1.0 kg/day is optimal to avoid side effects because only 750 to 900 mL/day of fluid can be mobilized from the abdomen into the general circulation. After the ascites is mobilized by whatever method, diuretic therapy should be adjusted to keep the patient free of ascites.

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 hepatic encephalopathy (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 in patients with cirrhosis and tense ascites who are treated with repeated large-volume or total paracentesis, and it has been shown in randomized trials to prevent hyponatremia and renal impairment. Partial mobilization of ascites, for example, 5 L (at least in edematous patients), can be removed safely without the infusion of albumin. However, complete mobilization of ascites without plasma volume expansion causes a deterioration in systemic hemodynamics in all patients, and 20% will develop hyponatremia or renal dysfunction that is frequently irreversible. Generally, 8 to 10 g of albumin is infused for every 1 L of ascites that is removed. Dextran 70 or polygeline is less effective than albumin as a plasma volume expander. Terlipressin may be an alternative to albumin, but it is not available in the United States.

Refractory Ascites

Definition

Refractory ascites is due to avid renal retention of sodium, which occurs with decompensated cirrhosis and in 10% to 20% of patients. Clinically, ascites is considered to be refractory when a patient has adequate sodium restriction and receives maximal tolerable doses of diuretics without desired weight loss (24-hour urine sodium is less than

intake). Patients who have not had a response to 400 mg/day of spironolactone and 160 mg/day of furosemide generally have ascites refractory to medical therapy.

Reversible factors that contribute to sodium retention should be identified and corrected (Table 3).

Treatment Options

The long-term prognosis after the development of refractory ascites is dismal, with a high 1-year mortality rate (>70%). Liver transplantation is the only therapeutic modality capable of improving both the quality of life and patient survival. Consequently, liver transplantation should always be considered in an otherwise acceptable candidate with ascites that cannot be controlled with adequate sodium restriction and diuretic therapy.

Other therapeutic options for refractory ascites are 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 therapy for more than 2 or 3 months. TIPS is relatively contraindicated for patients who are older than 70 years, have cardiac dysfunction, or have a Child-Turcotte-Pugh (CTP) score higher than 11.

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.

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; mortality increases for patients with a pre-TIPS CTP score higher 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. Covered stents may prove to require less revision and to be associated with better survival and less encephalopathy. However, the optimal hepatic venous pressure gradient for control of ascites is not known.

Table 3. 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

Hepatic Hydrothorax

This 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. It generally is considered that intestinal bacterial translocation is 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 (PSE). Patients with cirrhosis who are at particular risk for spontaneous bacterial peritonitis are those with advanced cirrhotic-stage liver disease, a low concentration of ascitic fluid protein (<1 g/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 (Fig. 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 confirming that the culture is positive.

A presumptive diagnosis of spontaneous bacterial peritonitis is made with the finding of more than 250 PMNs per milliliter of ascitic fluid in a patient with cirrhotic ascites and no secondary source of infection. Confirmation is by positive bacterial

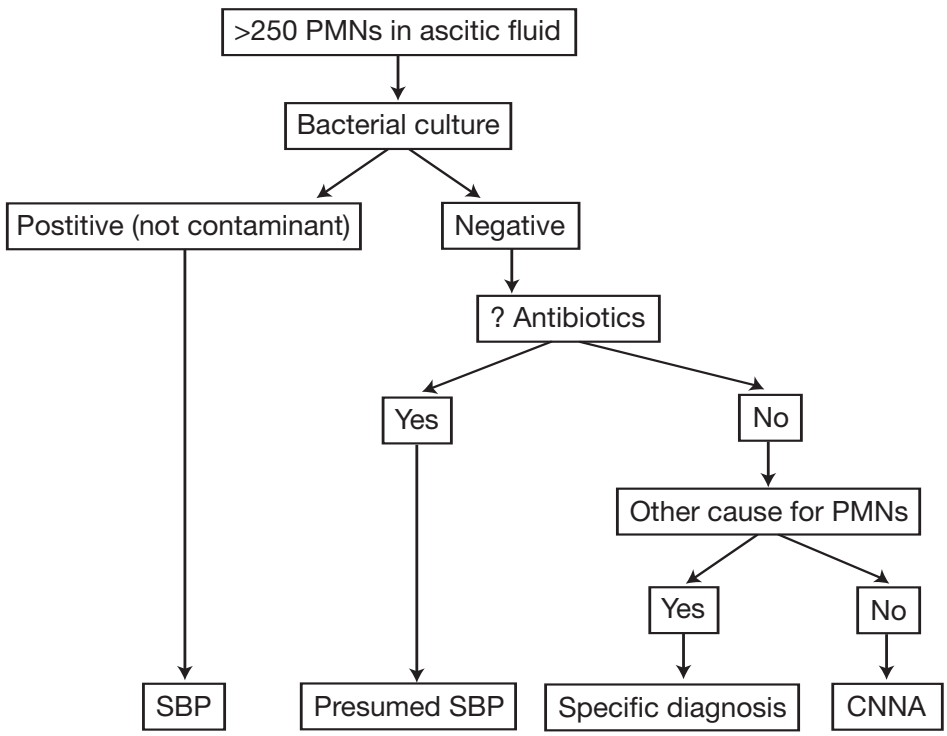

Fig. 1. Diagnostic algorithm for spontaneous bacterial peritonitis. CNNA, culture-negative neutrocytic ascites; PMN, polymorphonuclear neutrophil; SBP, spontaneous bacterial peritonitis.

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 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, empiric therapy for spontaneous bacterial peritonitis must be instituted and directed against aerobic enteric bacteria. Cefotaxime, 1 to 2 g intravenously every 8 hours, is the first choice of antibiotic for empiric therapy and is started when the PMN count in ascitic fluid is more than 250 cells/mL. This therapy is more effective (86%) than the combination of ampicillin-aminoglycoside 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 has been found to be clinically effective in more than 80% of cases. After the organism has been identified, antibiotic therapy can be adjusted accordingly. Uncomplicated spontaneous bacterial peritonitis may be treated effectively in an outpatient setting with oral ofloxacin, a much less expensive alternative.

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. This is an important predictor of mortality for these patients. A randomized trial has shown that albumin infusion on day 1 (1.5 g of albumin per kilogram) and day 3 (1 g/kg) prevented this complication. Albumin infusions are now the recommended therapy for spontaneous bacterial peritonitis. However, because of the expense of albumin, some physicians argue that perhaps this approach should be reserved for patients who are very ill, especially those with a bilirubin level more than 4 mg/dL and an increased creatinine level.

Repeat Paracentesis

The usefulness of diagnostic paracentesis after 48 hours of antibiotic therapy to observe the PMN response is debated. Repeat paracentesis "provides evidence of a satisfactory response to antibiotic therapy and is mandatory" for patients who do not show clinical improvement. If the PMN count is greater than 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, most commonly from a perforated viscus or, in about 15% of cases, an abscess. The operative mortality rate for patients with cirrhosis who have infected ascites is about 85%, but is 100% for patients with secondary bacterial peritonitis without surgery. 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 glucose level less than 50 mg/dL, lactate dehydrogenase level greater than the upper limit of normal for serum, and an increase in the number of PMNs in ascitic fluid despite antibiotic therapy.

Primary Prophylaxis

A disadvantage of antibiotic prophylaxis is the emergence of drug-resistant bacteria, as mentioned above. Episodes of bleeding in patients with Child's class C cirrhosis or recurrent bleeding in patients with cirrhosis are factors that predict infection and spontaneous bacterial peritonitis, which are often severe. Oral or systemic antibodies should be given for 7 days to all patients with cirrhosis who have an episode of gastrointestinal tract bleeding. Whether antibiotic prophylaxis is beneficial in patients with cirrhosis who have very low levels of protein (<10 g/L) in the ascitic fluid is debated, and no consensus exists.

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 liver transplantation), and only occasionally does diuretic therapy completely clear the ascites. Treatment with norfloxacin, 400 mg/day, 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 have also been effective for prophylaxis.

Bacterascites

When diagnostic paracentesis shows no evidence of neutrocytic ascites (<250 PMNs/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) PMNs >250/mL, treat as spontaneous bacterial peritonitis; 2) PMNs <250/mL but again culture-positive, treat with antibiotics; and 3) PMNs <250/mL but negative cultures, no treatment.

RENAL FUNCTION ABNORMALITIES IN CIRRHOSIS AND HEPATORENAL SYNDROME

The hemodynamic changes in chronic liver disease increasingly worsen with the progression from compensated cirrhosis, to ascites, 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 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, hence the renal vasoconstriction of hepatorenal syndrome. Cardiac output increases in cirrhosis, but eventually as hemodynamic changes worsen, cardiac output decreases, further worsening the blood flow to extrasplanchnic organs and potentiating renal impairment.

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. However, symptoms are rare until sodium levels are very low (<110-115 mEq/L). Treatment is fluid restriction. Rarely do patients need infusion of hypertonic (3%) saline, and this is administered only to patients with severe, symptomatic hyponatremia. The aquaretic drug conivaptan, an antagonist of arginine vasopressin V_{1A} and V_2 receptors, is available in intravenous form in the United States, but it has not been evaluated systematically in cirrhosis. It may be considered for the patients hospitalized with cirrhosis and severe refractory hyponatremia.

Major Diagnostic Criteria for Hepatorenal Syndrome

The International Ascites Club has proposed that the presence of all the following major criteria is necessary for the diagnosis of hepatorenal syndrome:

- Chronic or acute liver disease with advanced liver failure and portal hypertension
- Low glomerular filtration rate, with the serum creatinine level greater than 1.5 mg/dL or creatinine clearance less than 40 mL/minute
- Absence of shock, bacterial infection, nephrotoxic drugs, or significant fluid loss
- No sustained improvement in renal function following diuretic withdrawal or plasma volume expansion
- Proteinuria of less than 500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

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/day), 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 (<30 mEq/L).

Hepatorenal Syndrome Types 1 and 2

Type 2 hepatorenal syndrome is moderate renal failure that is stable over a long time; 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 per day. 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 per day.

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, excessive use of diuretics, 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 renal failure in cirrhosis and is associated with arterial underfilling and renal vasoconstriction.

Renal prostaglandins oppose the renal vascular effects of vasoconstrictors such as angiotensin II and epinephrine, and local renal production of prostaglandins increases in cirrhosis, thus maintaining renal perfusion and sodium excretion. In advanced liver disease, renal compensatory mechanisms are lost (hepatorenal syndrome). This mechanism explains the nephrotoxicity of nonsteroidal antiinflammatory drugs (inhibitors of prostaglandin production) in cirrhosis.

Treatment

The only therapy proven effective for hepatorenal syndrome is liver transplantation. In type 2 hepatorenal syndrome, discontinuation of diuretics and plasma volume expansion are usually effective, at least temporarily. In established hepatorenal syndrome type 1, patients should undergo plasma volume expansion with albumin to a normal central venous pressure. A further fluid challenge may be tried but usually will be ineffective.

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/day) for type 1 hepatorenal syndrome. Terlipressin is the most widely studied drug and is safe. This has been administered in doses of 0.5 mg/4 hours, up to 12 mg/day, to more than 154 patients, with a response rate of 50% to 60%. However, this drug is not available in the United States. α_1-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.

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.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is the one complication of cirrhosis for which little progress has been made in understanding it, diagnosing it, and treating it. The diagnosis is still clinical, with no confirmatory laboratory testing. Therapies are very limited and nonspecific. Furthermore, no weight is given for this complication in the MELD system for organ allocation, resulting in considerable morbidity.

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 a neuropsychometric syndrome called *hepatic encephalopathy*. The pathophysiologic mechanism is not well understood, but the major toxins appear to be ammonia and endogenous substances that act at γ-aminobutyric acid-benzodiazepine receptors in the brain.

Clinical Features

Hepatic encephalopathy 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. Psychomotor speed, visual perception, and attention often are affected more than verbal ability, especially in "minimal" cases. Studies have now shown that even minimal PSE can greatly affect a patient's functioning both at home and at work, and its significance should not be underestimated. Also, there is evidence that these patients are not fit to drive a car.

The four stages of hepatic encephalopathy 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

No laboratory test can confirm the diagnosis, which rests entirely on clinical grounds in the setting of established chronic liver disease. An early battery of testing can be useful for "subclinical" cases, including number connection tests, line drawing test, serial dotting test, and digit symbol test. However, this testing is costly and time consuming. Asterixis is a nonspecific clinical sign, which generally, but not invariably, occurs in the early stages of encephalopathy. Although associated with an increased arterial level of ammonia, there is no correlation between the degree of encephalopathy and the ammonia level. Characteristic slow waves occur on the electroencephalogram.

Management

Identification of Precipitants

Hepatic encephalopathy must be differentiated from other causes of encephalopathy in patients with cirrhosis. Head imaging excludes structural causes of coma. Also, well-recognized precipitating factors must be sought and treated. To treat or avoid hepatic encephalopathy in patients who have advanced cirrhosis, the following general measures must be considered:

- Avoidance of analgesics, sedatives, and tranquilizers
- Control of gastrointestinal tract bleeding and purging of blood from the gastrointestinal tract
- Screening and aggressive therapy for any infection
- Correction of acidosis, alkalosis, hypoxia, or electrolyte abnormalities
- Prevention of constipation and intravascular volume depletion
- Adequate intake of glucose to treat hypoglycemia and prevent endogenous protein breakdown

- Adequate vitamin supplementation, including thiamine and folate

Treatment

Lactulose

This is the mainstay of therapy for most patients. Lactulose is a nonabsorbable synthetic disaccharide metabolized by colonic bacteria to organic acids. It acts as an osmotic laxative. Lactulose may stimulate bacterial growth, thereby increasing the incorporation of nitrogen, and the low pH of the organic acids may increase peristalsis. 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. Lactose is effective in lactase-deficient patients.

Antibiotics

Rifaximin is a new nonabsorbable antibiotic, which in doses of 400 mg 3 times daily, has shown some efficacy in the treatment of hepatic encephalopathy. It presumably acts by decreasing bacterial flora and, thus, reducing the formation of ammonia and other nitrogenous waste products. 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 PSE, but fewer than 10% of cases of PSE are associated with increased protein ingestion, and some studies have shown improvements in PSE in patients with better nutritional status and increased protein intake. Most patients with PSE do not need protein restriction. In advanced coma, protein is withheld for a short time while an adequate level of glucose is maintained with intravenous infusion; the precipitating cause for the PSE 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. Also, a small subset of patients appear to be "protein-sensitive," that is, they become encephalopathic with moderate amounts of protein. Thus, 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, within animal proteins, toxicity increases from dairy proteins to fish, to meat, and finally, to 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. For patients who are transplant candidates, mild PSE is tolerated better in the long term than a negative protein balance. For nontransplant candidates with end-stage liver disease and refractory PSE, 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 PSE. Trials that studied zinc therapy in PSE have been inconclusive. Preliminary studies are being conducted with ornithine-aspartate, which provides substrate for urea formation and glutamine synthesis (the two major routes of ammonia clearance). Benzoate and phenylacetate are used to correct urea cycle deficiencies, and some studies have shown benzoate to be beneficial in PSE. Intravenous flumazenil has produced temporary improvement in some patients with grade 4 coma, but the majority of patients probably do not benefit from it.

Portosystemic Encephalopathy After TIPS

Most post-TIPS PSE is maximal during the first 3 months and can be controlled by the above measures. About 8% of cases are refractory to medical treatment, and the options are liver transplantation 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 absorbent recirculating system has been used recently to treat patients who have acute decompensation of cirrhosis and PSE. It appears to be safe and has produced some biochemical and hemodynamic improvements.

Liver Transplantation

This is the ultimate therapy for PSE. PSE, which is recurrent or difficult to treat, is but one manifestation of a deteriorating liver and is an indication to consider orthotopic liver transplantation. Because hepatic encephalopathy 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.

Hepatic Encephalopathy and Spontaneous Portosystemic Shunts

A new area of investigation in PSE has been the identification of large portosystemic shunts in patients with recurrent or persistent PSE out of proportion to the severity of liver disease. Fourteen patients with recurrent or persistent PSE were studied and compared with patients with cirrhosis of equal severity (same bilirubin, international normalized ratio, albumin, sodium, and creatinine values and MELD score). As expected, patients with hepatic encephalopathy had higher ammonia levels but less ascites and varices, and, on spiral computed tomography, 71% had large portosystemic shunts compared with 14% of controls. The conclusion of the study was that the large shunts clearly decompress the portal circulation but perpetuate the hepatic encephalopathy. As yet, there are no proven therapeutic implications of this finding.

PROGNOSTIC INDICATORS FOR SURVIVAL IN CIRRHOSIS

Cirrhosis can be considered in four 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; however, varices are present but not ascites; the mortality rate is a little higher and 10% of patients have progression to a higher stage. Stage 3 is defined by the presence of ascites, with or without varices, and the mortality rate is 20%, with 7% of patients developing bleeding varices. Stage 4 is defined by bleeding varices; it has a higher mortality rate. CTP and MELD scores both predict mortality.

RECOMMENDED READING

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CHAPTER 28

Metabolic Liver Disease

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Metabolic liver disease encompasses a diverse group of disorders that can cause liver damage through various mechanisms. Many are due to inborn errors of metabolism that are relatively uncommon. The various metabolic liver diseases are listed in Table 1. This chapter reviews hereditary hemochromatosis, Wilson's disease, and α_1-antitrypsin (AAT) deficiency because they are the metabolic liver diseases most gastroenterologists are likely to encounter. These three disorders are compared in Table 2.

HEREDITARY HEMOCHROMATOSIS

Hereditary hemochromatosis is an autosomal recessive disorder associated with increased intestinal absorption of iron and the deposition of excessive amounts of iron in the liver, pancreas, and other organs. 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.

Not all iron overload is due to hereditary hemochromatosis, which should be distinguished

Table 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's disease
Niemann-Pick disease
Inborn errors of bile acid metabolism
Byler disease
Benign recurrent cholestasis
Inborn errors of copper metabolism
Wilson's disease
Inborn errors of iron metabolism
Hereditary hemochromatosis
Unclassified
α_1-Antitrypsin deficiency
Cystic fibrosis

Modified from Ghishan FK. Inborn errors of metabolism that lead to permanent hepatic injury. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. 4th ed. Philadelphia: Saunders; 2003. p. 1397-1459. Used with permission.

Abbreviations: AAT, α_1-antitrypsin; OLT, orthotopic liver transplantation.

Table 2. Comparison of Hemochromatosis, Wilson's Disease, and α_1-Antitrypsin Deficiency

Feature	Hemochromatosis	Wilson's disease	α_1-Antitrypsin deficiency
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal codominant
Homozygote frequency	1:200-300	1:30,000	1:2,000
Heterozygote frequency	1:10	1:100	1:30
Gene	*HFE*	*ATP7B*	
Number of mutations*	2 (C282Y, H63D)	>100	
Chromosome	6	13	14
Diagnosis	Transferrin saturation, ferritin, liver iron concentration, *HFE* gene test	Ceruloplasmin, slit-lamp exam for Kayser-Fleischer rings, urine and liver copper quantification	α_1-Antitrypsin phenotype
Treatment	Phlebotomy	Penicillamine, trientine, or zinc	None/orthotopic liver transplantation

**Clinically significant.*

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. Rarely, 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. Even high tissue concentrations of iron can be seen in some patients who have advanced cirrhosis due to causes other than hereditary hemochromatosis. In secondary iron overload, iron often accumulates in Kupffer cells rather than in hepatocytes, as typical of hereditary hemochromatosis. However, severe iron overload from hereditary hemochromatosis may be indistinguishable from that due to secondary causes.

The *HFE* Gene

The gene associated with hereditary hemochromatosis is the *HFE* gene. It is located on the short arm of chromosome 6. The two commonly assessed point mutations are C282Y and H63D. Other mutations have been described, but they are rare and not likely to be of major clinical importance. About 90% of patients with iron overload consistent with hereditary hemochromatosis have homozygosity for C282Y.

The greatest risk for iron overload is in persons homozygous for the C282Y mutation. Iron overload also occurs in a small proportion of persons with other *HFE* mutations (especially compound heterozygotes who have one copy of C282Y and one copy of H63D and occasionally H63D homozygotes), but it is usually less severe. Approximately 1% to 2% of the white population are compound heterozygotes or H63D homozygotes, and only a small percentage of these persons develop problems with iron overload. In addition, 20% of the US population is heterozygous for H63D. A single copy of H63D does not appear to be a risk factor for

the development of iron overload. Also, it should be remembered that clinically important iron overload can occur in the absence of *HFE* gene mutations. Therefore, a negative *HFE* gene test does not exclude iron overload.

Novel Genes and Proteins

Several other genes and proteins of iron metabolism have been discovered recently, including ferroportin, transferrin receptor 2, hemojuvelin, and hepcidin. Ferroportin is an iron exporter located on enterocytes, macrophages, and the hepatocyte basolateral membrane, and mutations in its gene have been associated with an autosomal dominant form of iron overload. Transferrin receptor 2 is located mainly on hepatocytes, and mutations in its gene *TFR2* have led to a rare autosomal recessive form of iron overload. Hemojuvelin (*HJV*) is the recently discovered gene for juvenile hemochromatosis located on chromosome 1q.

Of all the proteins, the one that has generated the most interest is hepcidin, a small polypeptide produced in the liver. Hepcidin inhibits iron absorption in the small intestine and prevents the release of iron from macrophages. It may function as a regulator of iron stores. Hepcidin levels are increased markedly in infectious and inflammatory conditions. It may be responsible for the development of anemia of inflammation (anemia of chronic disease). Hepcidin levels are inappropriately low in hereditary hemochromatosis, and hepcidin knockout mice develop iron overload in a pattern similar to that of human hereditary hemochromatosis. Preliminary studies have found that mutations in hepcidin may influence disease expression in hereditary hemochromatosis. This has led to reconsideration of the pathophysiology of iron metabolism. Previous models emphasized the role of enterocyte crypt cells in sensing body iron stores. It may be that the liver is the primary site for sensing the body iron stores, and it responds by increasing or decreasing the production of hepcidin. Future studies of hepcidin and other proteins of iron metabolism undoubtedly will clarify the pathophysiology of iron metabolism and hereditary hemochromatosis.

Clinical Features

Persons with hereditary hemochromatosis absorb only a few milligrams of iron each day in excess of the amount needed. Therefore, clinical manifestations generally occur after the fifth decade, when 15 to 40 g of iron have accumulated (normal body iron stores are approximately 4 g). Of those with C282Y homozygosity, about 30% of males and 2% to 10% of females have evidence of biochemical or clinical iron overload. Clinical expression is influenced by age, sex, iron content of the diet, blood loss as occurs in menstruation and pregnancy, and unknown factors, including mutations in genes other than *HFE*. Thus women, despite an equal frequency of homozygosity, express the disease less frequently than men. Other factors such as alcohol and hepatitis C may accelerate disease expression.

The classic description of hereditary hemochromatosis is cutaneous hyperpigmentation, diabetes mellitus, and cirrhosis ("bronze diabetes"). Other clinical manifestations include fatigue, abdominal pain, hepatomegaly, abnormal liver enzyme levels, hepatocellular carcinoma, cardiomyopathy, cardiac conduction disorders, hypothyroidism, hypogonadism, impotence, and arthropathy. An example of hemochromatosis arthropathy is shown in Figure 1.

In the past, hereditary hemochromatosis usually was diagnosed at an advanced stage. Currently, most patients with newly diagnosed hereditary hemochromatosis are asymptomatic. This shift toward earlier diagnosis probably is due partly to increased physician awareness and the decision of some providers to screen for disease with serum iron tests. The most common symptoms are fatigue, arthralgias, and impotence. Most, if not all, clinical manifestations are preventable if the disease is diagnosed early and treated appropriately. Some of its manifestations, such as skin bronzing, cardiomyopathy, cardiac conduction disorders, hepatomegaly, and abnormal liver test results, frequently are reversible after excess iron stores have been removed. Most of the other clinical manifestations are not reversible.

Diagnosis

The diagnosis of hereditary hemochromatosis is made on the basis of a combination of clinical, laboratory, and pathologic criteria, including an increase in serum transferrin saturation [100 × (serum iron concentration ÷ total iron binding capacity)] and an increase in the serum concentration

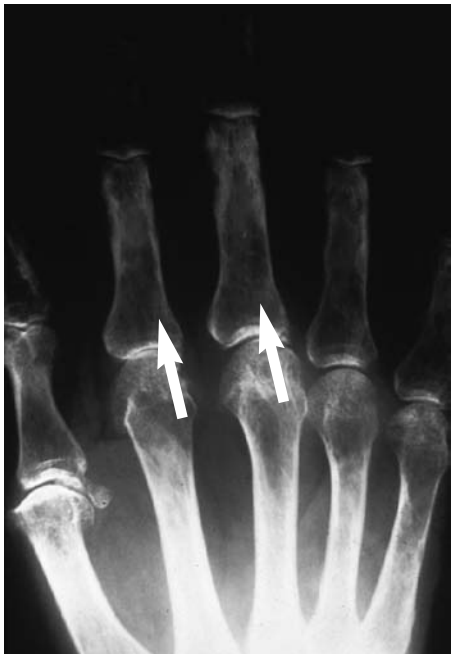

Fig. 1. Hemochromatosis arthropathy. A radiograph of the hand shows cartilage loss, marginal sclerosis, and osteophyte formation in the second and third metacarpophalangeal joints (*arrows*) without involvement of the fourth and fifth joints. Involvement of the second and third metacarpophalangeal joints is characteristic of hemochromatosis arthropathy. Occasionally, calcium pyrophosphate dihydrate crystals may be present (chondrocalcinosis). (Modified from Riely CA, Vera SR, Burrell MI, Koff RS. The gastroenterology teaching project, unit 8—inherited liver disease. Used with permission.)

of ferritin. There is diurnal variation in serum iron values, and measurements may be affected by the ingestion of food; therefore, if transferrin saturation is increased, the measurement should be repeated in the early morning with the patient fasting. An increase in transferrin saturation is the earliest phenotype abnormality in hereditary hemochromatosis.

The serum concentration of ferritin usually provides a reasonable estimate of total body iron stores, but it is also an acute phase reactant and is increased in various infectious and inflammatory conditions in the absence of iron overload. 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 2. The *HFE* gene test is most useful for surveillance of adult first-degree relatives of an identified proband. Screening for the disease in family members is crucial because 25% of siblings and 5% of children of a proband will have the disease. *HFE* gene testing should replace the more cumbersome and expensive HLA typing previously used to screen for hereditary hemochromatosis in siblings. Also, *HFE* gene testing is often useful in helping to resolve ambiguous cases, such as iron overload associated with hepatitis C, alcoholic liver disease, or other causes of end-stage liver disease. *HFE* gene testing should be considered also for siblings of C282Y heterozygotes. Before the *HFE* gene test is performed, the person should be counseled about the risks, benefits, and alternatives of genetic testing. Although rare, the possibility of insurance, employment, or other discrimination based on *HFE* test results is a concern. For this reason, *HFE* gene testing usually is not recommended for anyone younger than 18 years. The spouse of an affected person may be tested to assess risk to children. If the spouse does not have a mutation for *HFE*, the children will not be affected.

Before the *HFE* gene test was available, liver biopsy often was used to confirm the diagnosis of hereditary hemochromatosis. Hepatic iron may be assessed with an iron stain such as Perls' Prussian blue. In hereditary hemochromatosis, iron initially accumulates in periportal hepatocytes, but eventually it is distributed throughout the liver. In secondary iron overload, iron often is present predominantly in Kupffer cells, which may help distinguish it from hereditary hemochromatosis. In severe iron overload, this distinction cannot be made. The histologic features of the liver in hereditary hemochromatosis and secondary iron overload are shown in Figure 3.

In hereditary hemochromatosis, iron stores in the liver increase progressively with age. This has led to the development of the *hepatic iron index*, which is the hepatic iron concentration in micromoles/gram dry weight liver divided by the patient's age in years. Originally, this index was intended to distinguish between hereditary hemochromatosis homozygotes and heterozygotes and persons with alcoholic liver disease. In the

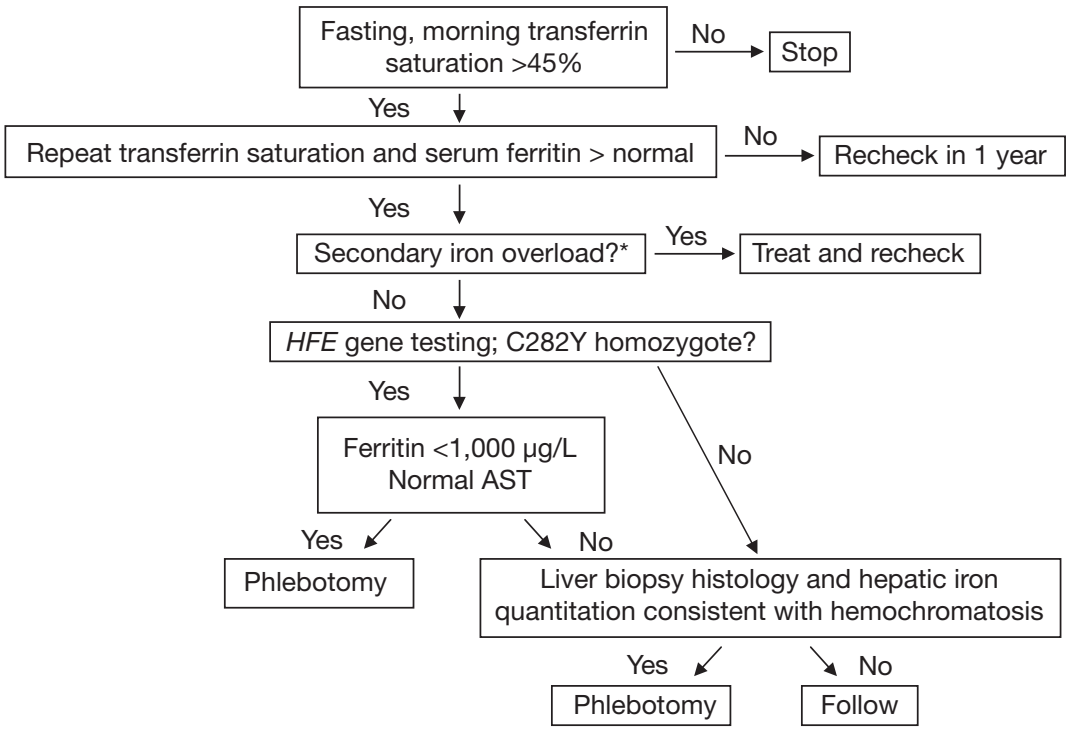

Fig. 2. Diagnostic algorithm for hereditary hemochromatosis. AST, aspartate aminotransferase. *Anemias with ineffective erythropoiesis, multiple blood transfusions, or oral/parenteral iron supplements. (Modified from Brandhagen DJ, Fairbanks VF, Batts KP, Thibodeau SN. Update on hereditary hemochromatosis and the *HFE* gene. Mayo Clin Proc. 1999;74:917-21. By permission of Mayo Foundation for Medical Education and Research.)

initial study, the hepatic iron index was greater than 1.9 for all homozygotes and less than 1.9 for all heterozygotes or patients with alcoholic liver disease. A hepatic iron index greater than 1.9 is not diagnostic of hereditary hemochromatosis because patients with severe iron overload of any cause may have an index greater than 1.9. Also, because hereditary hemochromatosis is increasingly diagnosed at an earlier stage, not all homozygotes will have a hepatic iron index greater than 1.9.

Treatment

The treatment of hereditary hemochromatosis usually is reserved for patients with evidence of iron overload as indicated by an increase in the serum concentration of ferritin. Therapeutic phlebotomy is the preferred treatment because it is simple, relatively inexpensive, and effective. It 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 above a preselected value (usually 12-13 g/dL). If the concentration is below the preselected value, phlebotomy should not be performed. Once the hemoglobin concentration remains below the preselected value for three 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 greater than 50 µg/L, with a transferrin saturation in the low-normal range. Once iron depletion has been achieved, most patients require four to eight "maintenance" phlebotomies annually to keep the ferritin level lower than 50 µg/L.

Generally, iron chelators such as the parenteral agent deferoxamine and oral agent deferasirox are not used to treat iron overload in hereditary hemochromatosis. Iron chelators are much less effective than phlebotomy in removing excess iron. They are administered sometimes to patients with

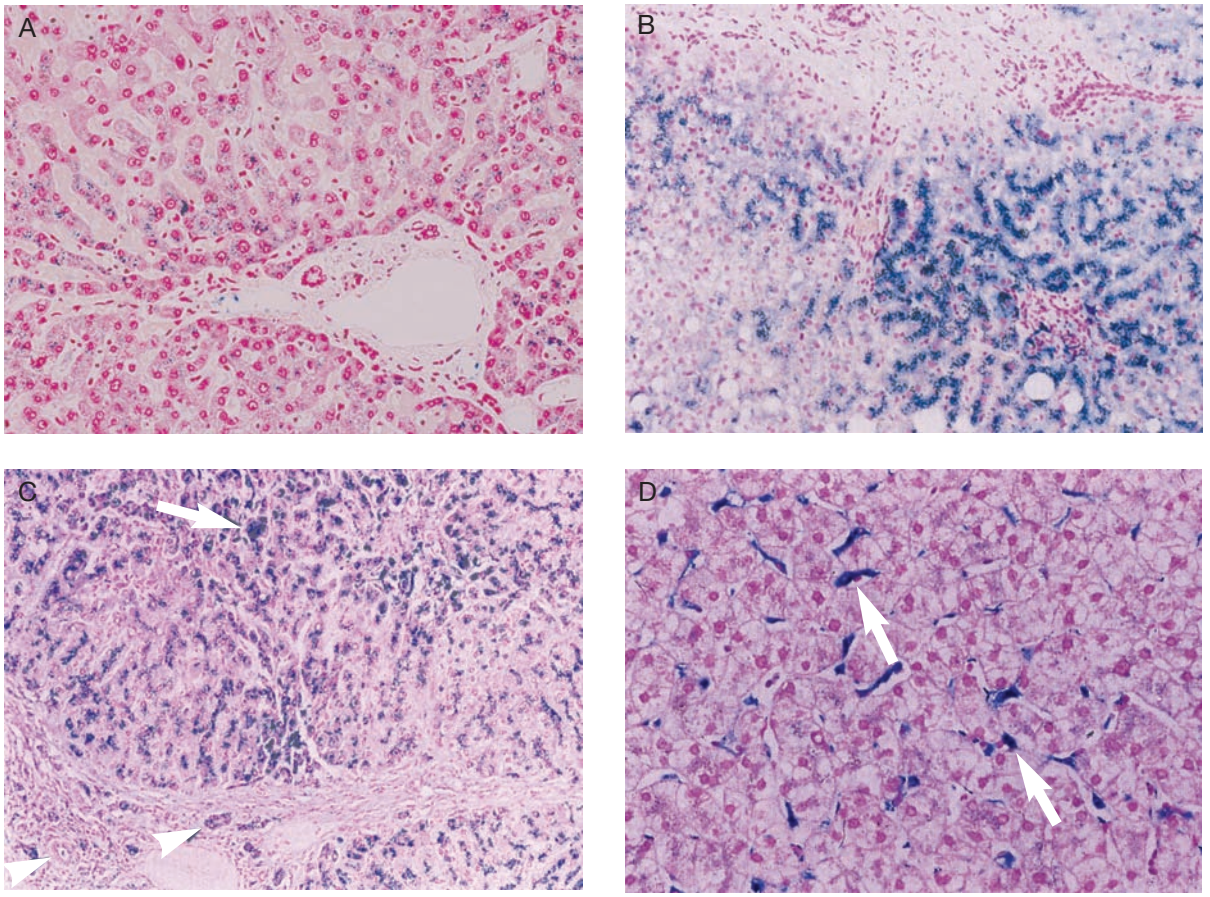

Fig. 3. Iron deposition in the liver. *A*, Mild (grade 1 of 4) iron deposition in hepatocytes. *B*, Moderate hemosiderin deposition in precirrhotic homozygous hemochromatosis. Zone 1 hepatocytes are predominantly involved, biliary hemosiderin is not evident, and fibrosis has not yet occurred—all indicating relatively early precirrhotic disease (liver iron concentration, 10,307 µg Fe/g dry weight; iron index, 3.2). (Original magnification x133.) *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 x133.) *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 x240.) *A-D*, Perls' Prussian blue stain. (*A* from Brandhagen DJ. Liver transplantation for hereditary hemochromatosis. Liver Transpl. 2001;7:663-72. Used with permission. *B-D* 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; 2000. p. 187-99. Used with permission.)

iron overload due to hematologic disorders characterized by ineffective erythropoiesis and anemia, for which phlebotomy is not an option.

Patients with hereditary hemochromatosis should refrain from taking iron supplements, including multivitamins with iron, and high-dose vitamin C supplements. A "low iron diet" is not necessary, but red meat should be consumed in moderation. Patients also should avoid consuming raw seafood because of an increased risk of *Vibrio vulnificus* infection. Also, poorly cooked meat should be avoided, and patients should avoid alcohol or minimize its intake because iron and alcohol are synergistic hepatotoxins.

Despite being common, hereditary hemochromatosis only rarely causes complications of portal hypertension and is an uncommon indication for orthotopic liver transplantation (OLT), accounting

for fewer than 1% of all liver transplants performed in the United States. The survival rate of patients with hereditary hemochromatosis undergoing OLT has improved in recent years and is now similar to that of OLT for other indications. Many deaths of liver transplant recipients who have hereditary hemochromatosis are caused by cardiac or infectious complications.

Prognosis

For patients in whom hereditary hemochromatosis is diagnosed and treated before diabetes mellitus and cirrhosis develop, the age- and sex-adjusted survival rate is normal. However, when cirrhosis or diabetes develops, survival decreases markedly. Up to one-third of patients with hereditary hemochromatosis and cirrhosis develop hepatocellular carcinoma, which often is the cause of death. The presence of hemochromatosis imparts a 200-fold increased risk for the development of liver cancer, with most cases involving patients with cirrhosis.

The Role of Liver Biopsy

HFE gene testing eliminates the need for liver biopsy in many patients. Traditionally, liver biopsy was performed in patients with iron overload to confirm the diagnosis of hereditary hemochromatosis and to exclude cirrhosis. In patients with iron overload who are C282Y homozygotes, liver biopsy is not necessary to confirm the diagnosis. However, liver biopsy is still the "gold standard" for assessing the degree of fibrosis. Definitively excluding cirrhosis is important because of the increased risk of the development of hepatocellular carcinoma and the resulting need for surveillance. The risk for cancer persists even after excess iron stores have been depleted. For patients with cirrhosis, surveillance with ultrasonography and α-fetoprotein every 6 months is recommended.

There may be a subset of patients with hereditary hemochromatosis whose risk of cirrhosis is minimal, and liver biopsy would be unnecessary. Several studies have confirmed that certain noninvasive predictors are accurate in excluding cirrhosis in C282Y homozygotes. In these studies, there were virtually no cases of cirrhosis in C282Y homozygotes who had a serum concentration of ferritin less than 1,000 µg/L and a normal aspartate aminotransferase value. A serum concentration of ferritin less than 1,000 µg/L seems to be the best predictor of the absence of cirrhosis in C282Y homozygotes. However, the positive predictive value of a serum concentration greater than 1,000 µg/L is poor because only about 50% of those with this value had cirrhosis. Consequently, liver biopsy is advisable for patients 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. Similar information is not available for non-C282Y homozygotes. Liver biopsy may be necessary for this group of patients to confirm the diagnosis and to exclude cirrhosis.

Screening for Hemochromatosis

Currently, experts disagree about the usefulness of screening for 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. They cite lack of information about the burden of disease and disease expression in those with *HFE* mutations as reasons for not endorsing population screening. However, the natural history of the disease in an asymptomatic patient identified by population screening may never be known because many would consider it unethical to withhold treatment once iron overload develops.

Although the majority of C282Y homozygotes probably will not develop serious problems with iron overload, the true prevalence of clinically relevant disease manifestations in hereditary hemochromatosis is unknown. With the information currently available, it seems reasonable to screen for iron overload in persons with a family history of hereditary hemochromatosis symptoms or signs suggestive of the disease or chronic liver disease.

WILSON'S DISEASE

Wilson's disease is an autosomal recessive disorder characterized by abnormal intrahepatic copper metabolism and deposition of excess copper in the liver, brain, cornea, and other organs. Approximately 1/30,000 persons are homozygous and 1/100 are heterozygous carriers of a Wilson's disease gene mutation. It is likely that about only half of all persons with the disease have come to

medical attention. Not all cases of copper excess in the liver are due to Wilson's disease. Patients with chronic cholestatic biliary disorders such as primary biliary cirrhosis, primary sclerosing cholangitis, or biliary atresia often have excess copper levels in the liver, although usually not to the degree seen in Wilson's disease.

Copper Metabolism and Pathogenesis

Body copper homeostasis is achieved through biliary excretion. In Wilson's disease, intestinal copper absorption is normal but biliary excretion of copper is decreased. Copper toxicity has a major role in the pathogenesis of the disease. Copper accumulates in the liver as a result of an abnormal copper transport protein and eventually appears in other organs, particularly the brain. 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's disease; rather, it is an effect of the abnormal cellular trafficking of copper.

Genetics

The gene for Wilson's disease (*ATP7B*) was isolated in 1993. Located on chromosome 13, it codes for a copper-transporting P-type adenosine triphosphatase that is located in the endoplasmic reticulum and possibly the biliary canalicular membrane. Thus far, more than 100 mutations have been described. Attempts to correlate genotype with phenotype have not shown a consistent pattern. From 30% to 40% of North American and European patients have the H1069Q mutation. Unlike hereditary hemochromatosis, in which approximately 90% of cases are homozygous for the C282Y mutation, the majority of cases of Wilson's disease are compound heterozygotes (one copy of two different mutations). The number of clinically important mutations makes genetic testing less useful for this disease than for hereditary hemochromatosis.

Clinical Features

The variation in the clinical presentation of Wilson's disease is tremendous, ranging from asymptomatic patients to those with crippling neurologic symptoms. The usual age range at presentation is 12 to 23 years; the disease is extremely rare in patients older than 40 years . The five main categories of clinical presentation include hepatic, neurologic, psychiatric, hematologic, and ophthalmologic. In one large clinical series, the initial clinical manifestations were hepatic in 42% of patients, neurologic in 34%, psychiatric in 10%, and hematologic in 12%. Wilson's disease can simulate any syndrome of liver disease, including fulminant liver failure, chronic hepatitis, and cirrhosis. Liver manifestations tend to be more common in childhood, whereas neurologic symptoms tend to appear in the second and third decades. Although Wilson's disease should be considered in all young patients with liver disease, it is responsible for fewer than 5% of cases of chronic hepatitis in persons younger than 35 years. Fulminant liver failure due to Wilson's disease is four times more common in females than males. Reports of hepatocellular cancer in Wilson's disease are rare, even though many patients have advanced fibrosis at a young age.

Neurologic syndromes 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. Unfortunately, children often are classified as having behavioral problems until progressive and sometimes irreversible neurologic symptoms begin to develop.

Patients may present first with hemolytic anemia, frequently seen in association with acute, severe, or fulminant hepatitis. The constellation of young age, severe liver dysfunction, and hemolytic anemia should be assumed to be Wilson's disease until proved otherwise. Occasionally, the disease is identified because of incidental eye findings, either brown Kayser-Fleischer rings, representing copper deposition in the periphery of the cornea, or sunflower cataracts. The cataracts are seen only with a slit lamp and do not interfere with vision. The eye findings in Wilson's disease are shown in Figure 4. Renal manifestations include 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

The differential diagnosis of Wilson's disease is extensive and depends on the presenting clinical syndrome. The disease should be considered in any person younger than 30 years who has liver disease. Nonalcoholic steatohepatitis, autoimmune hepatitis, and chronic viral hepatitis are the most frequently considered alternative diagnoses. The combination of liver disease and extrapyramidal motor abnormalities should strongly suggest Wilson's disease. The combination of severe liver disease and hemolytic anemia should never be missed. Traditionally, the diagnosis requires at least two of the following: 1) Kayser-Fleischer rings, 2) low level of ceruloplasmin, 3) typical neurologic symptoms, and 4) liver copper concentration greater than 250 µg/g dry weight.

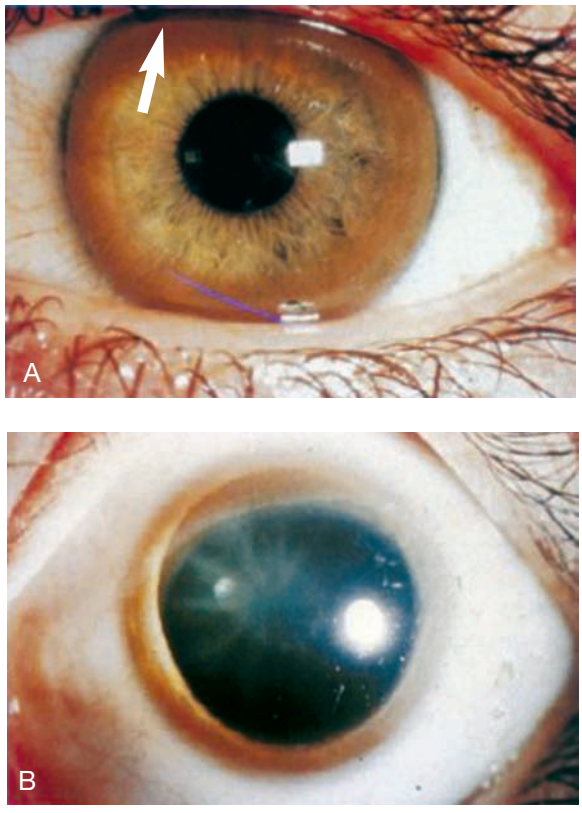

Fig. 4. *A*, Kayser-Fleischer ring (*arrow*). *B*, Sunflower cataract. (From Zucker SD, Gollan JL: Wilson's disease and hepatic copper toxicosis. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. 3rd ed. Philadelphia: WB Saunders; 1996. p. 1405-39. Used with permission.)

Kayser-Fleischer rings are seen in many patients with neurologic symptoms but are not found frequently in patients who have only liver disease. These rings have been detected also with a slit lamp in conditions associated with chronic cholestasis, such as primary biliary cirrhosis and sclerosing cholangitis. The serum level of ceruloplasmin is less than 20 mg/dL in 95% of patients with Wilson's disease. Even though the level of ceruloplasmin may 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's disease except in rare patients presenting with fulminant hepatitis. Persons who are heterozygous for the Wilson's disease gene may have a ceruloplasmin level less than 20 mg/dL but do not develop clinical disease. Almost any chronic liver disease in which liver synthetic function is decreased may be associated with a ceruloplasmin level that is lower than normal. The serum concentration of copper may be low, normal, or increased and, thus, is not particularly helpful. Although urinary copper excretion may be increased in other liver diseases, a value less than 100 µg/24 hours in a patient with clinical disease would be very unusual in symptomatic Wilson's disease. A low urinary copper excretion rate 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, particularly in those with a normal level of ceruloplasmin or without Kayser-Fleischer rings or neurologic symptoms. Often, steatosis is present, and glycogenated nuclei are common. Tissue analysis for copper is the "gold standard" for confirming the diagnosis of Wilson's disease. 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's disease may already have marked liver fibrosis; thus, liver biopsy should be strongly considered in children to stage the liver disease.

Biochemical tests often show characteristic patterns, but they are not consistent enough to be confirmatory. The alkaline phosphatase level may be low, and the aminotransferase levels tend to be increased less than would be expected from other signs of liver necrosis. In fulminant Wilson's disease, the uric acid level usually is low or undetectable, often because of concomitant proximal renal tubular acidosis. In fulminant liver failure, a marked increase in the serum level of copper strongly suggests the diagnosis of Wilson's disease, although a normal level does not exclude fulminant Wilson's disease. A diagnostic algorithm for Wilson's disease is provided in Figure 5. Complete gene sequencing is available; this may disclose a functionally significant mutation in a case in which the results of standard tests are equivocal.

Family Screening

As in hereditary hemochromatosis, screening should be directed at siblings because each has about a 25% chance of having Wilson's disease. If treatment is begun in the presymptomatic phase of the disease before cirrhosis is established, it is essentially curative. Because copper metabolism in infancy and early childhood may simulate Wilson's disease, children should not be tested before age 5 years. 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.

Treatment

"Decoppering" Agents

Penicillamine and trientine were developed as metal chelators and are approved for the treatment of Wilson's disease. Penicillamine is an effective first-line treatment, but up to 20% of patients experience drug toxicity, including hypersensitivity reactions, bone marrow suppression, proteinuria, autoimmune disorders, and dermatologic conditions. A starting dose of 250 to 500 mg/day is gradually increased to 1 to 2 g/day divided into two to four doses. The drug should be given with small doses of pyridoxine because it can deplete vitamin B_6. Treatment response 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 urine and serum levels of copper and the ceruloplasmin level should be measured and a complete blood count should be performed weekly during the first month, 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). As many as 20% of patients with neurologic symptoms may experience worsening of their symptoms during the first month of treatment. This deterioration has been irreversible in some patients.

Trientine was introduced as an alternative to penicillamine and 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 cupriuresis is less pronounced than with penicillamine, but an initial increase is expected. Also, trientine has a lower incidence of adverse effects and a lower rate of neurologic worsening at the start of treatment. Occasionally, iron deficiency may develop because of sideroblastic anemia.

Tetrathiomolybdate has shown promise as an effective decoppering agent, with approval still pending.

Inhibition of Copper Absorption

Zinc acetate, 50 mg 3 times daily, is effective therapy for presymptomatic patients and pregnant women. It also is an alternative maintenance therapy for patients presenting with symptomatic disease after 6 to 12 months of standard treatment for removal of copper. Zinc acetate induces the

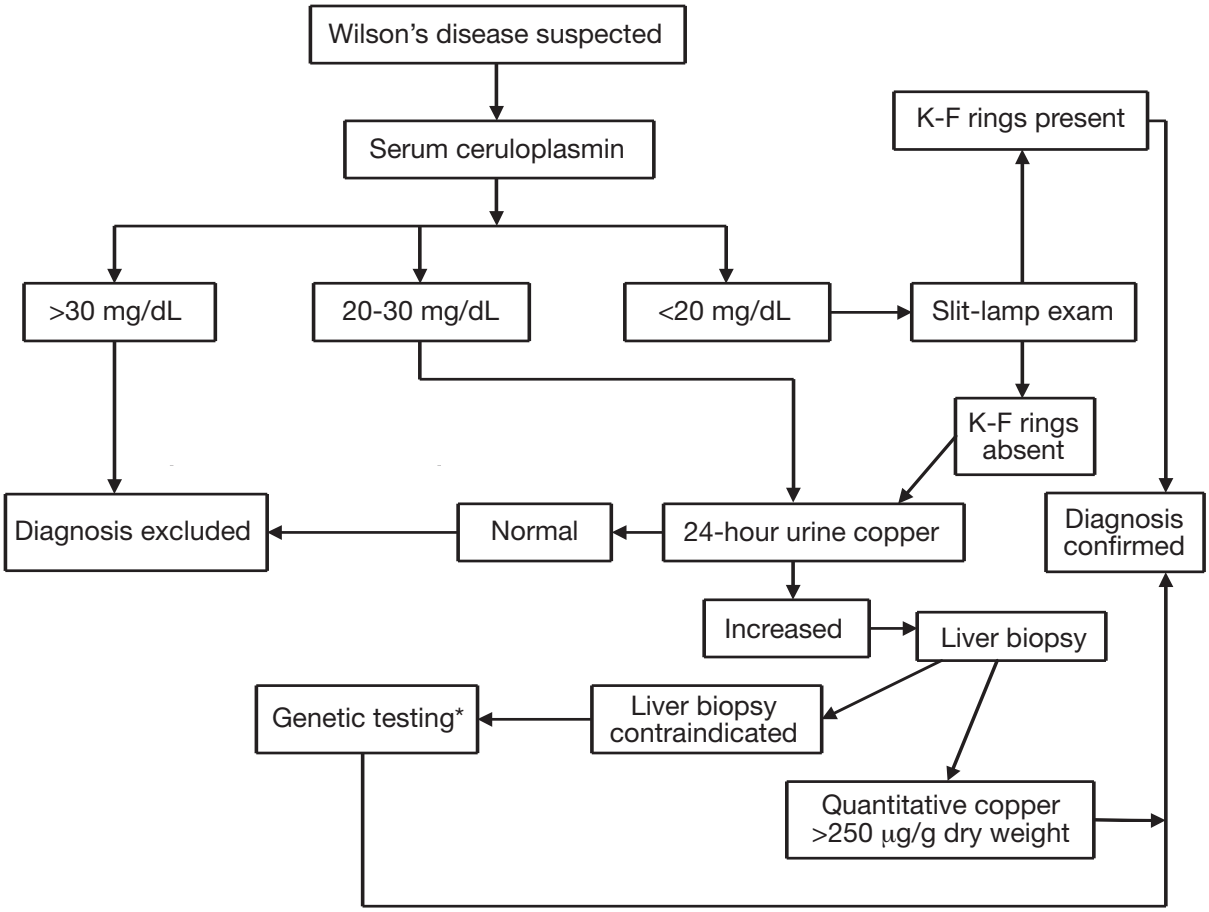

Fig. 5. Diagnostic algorithm for Wilson's disease. K-F, Kayser-Fleischer. *Genetic testing is performed within families when diagnosis is already established in one family member, using the index patient DNA as a reference. (Modified from Gollan JL, Zakko WF. Wilson disease and related disorders. 2nd ed. In: Friedman LS, Keeffe EB, editors. Handbook of liver disease. Philadelphia: Churchill Livingstone; 2004. p. 221-35. Used with permission.)

synthesis of metallothionein in the intestinal epithelium, which then preferentially binds copper and prevents its absorption. Treatment is monitored by checking urinary levels of zinc and copper. The urinary zinc excretion should be at least 2,000 μg/day.

For pregnancy, 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.

A problem with medical therapy for patients with Wilson's disease is compliance. It is hard to convince young people, many of whom feel well, of the need to take medicine 2 to 4 times daily for the rest of their lives. The tragedy is that if a patient stops treatment, the probability of death from fulminant liver failure within 1 to 2 years is very high, even if the patient was initially asymptomatic.

Transplantation

The indications for liver transplantation include fulminant liver failure, end-stage liver disease unresponsive to medical therapy, and chronic deterioration of liver function despite long-term therapy. Liver transplantation is curative because it corrects the metabolic defect in Wilson's disease. Transplantation is the treatment of choice for

fulminant liver failure because of the low probability that medical therapy will be effective. Nevertheless, medical therapy should be started because patients occasionally recover. Patients who received a liver transplant for fulminant hepatic failure have a 1-year survival rate of 73%; among those with chronic liver failure, the rate is about 90%. There are anecdotal reports of marked neurologic improvement after liver transplantation, but transplantation performed solely for refractory neurologic symptoms is considered experimental because of the limited experience and uncertain outcome.

α_1-ANTITRYPSIN DEFICIENCY

Genetics and Function

AAT deficiency is an autosomal codominant disorder characterized by lung and liver injury. AAT is a member of the serine protease supergene family. It functions to protect tissues from proteases such as neutrophil elastase. AAT is encoded by a gene on the long arm of chromosome 14. The phenotype Pi*MM (Pi, protease inhibitor) is present in 95% of the population and is associated with normal serum levels of AAT. For liver disease, the Z allele is the most clinically relevant. The homozygote frequency of the Z allele is 1:2,000, with a heterozygote frequency of 1:30. The Pi*ZZ phenotype is accompanied by a severe deficiency in AAT, and the Pi*MZ phenotype leads to intermediate deficiency.

Pathogenesis

The pathogenesis of liver disease associated with AAT deficiency likely is due to the accumulation of the mutant AAT protein in the endoplasmic reticulum. The abnormally folded protein is unable to exit the endoplasmic reticulum. Unlike the lungs, the liver is not damaged by the uninhibited effects of elastases and other proteolytic enzymes. This is supported by the observation that patients with two copies of the rare AAT null allele may develop lung disease but do not develop liver disease.

Clinical Features

AAT deficiency may cause premature emphysema and liver disease. In the only population-based study performed, the Swedish neonatal screening study identified 127 AAT-deficient children who were followed prospectively through age 18 years. Neonatal cholestasis developed in 11%, and 6% had other liver disease without jaundice. Liver test abnormalities developed 1 to 2 months after birth and usually normalized by 6 months. A small proportion of children developed end-stage liver disease or presented with fulminant liver failure in infancy. Most (83%) AAT-deficient children were healthy throughout childhood, although most had liver test abnormalities in early life. In adolescents and adults, AAT deficiency may cause hepatitis or cirrhosis. It has been estimated that 2% of adults between 20 and 50 years old with the Pi*ZZ phenotype will develop cirrhosis, compared with 19% of those older than 50. In adults, hereditary hemochromatosis is the most common inherited cause of cirrhosis, but AAT deficiency is the most common metabolic indication for OLT. It is debated whether persons with the Pi*MZ phenotype are at risk for the development of chronic liver disease. Several studies have noted an increased prevalence of the Pi*MZ phenotype among those undergoing OLT for cryptogenic cirrhosis compared with those having OLT for other indications. Patients with cirrhosis due to AAT deficiency have a greatly increased risk of hepatocellular carcinoma, with some studies reporting a prevalence of primary liver cancer of up to 30%.

Diagnosis

The diagnosis of AAT deficiency is made by AAT phenotyping or genotyping. Serum levels of AAT should not be used to diagnose AAT deficiency because they may be falsely increased in inflammatory conditions, malignancies, pregnancy, and with estrogen supplementation. Unlike lung disease, liver damage does not correlate with serum levels of AAT. The diagnosis is confirmed by liver biopsy. The characteristic finding is the presence of eosinophilic, periodic acid-Schiff–positive, diastase-resistant 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 does not imply liver disease. Furthermore, because the globules may be variably distributed throughout

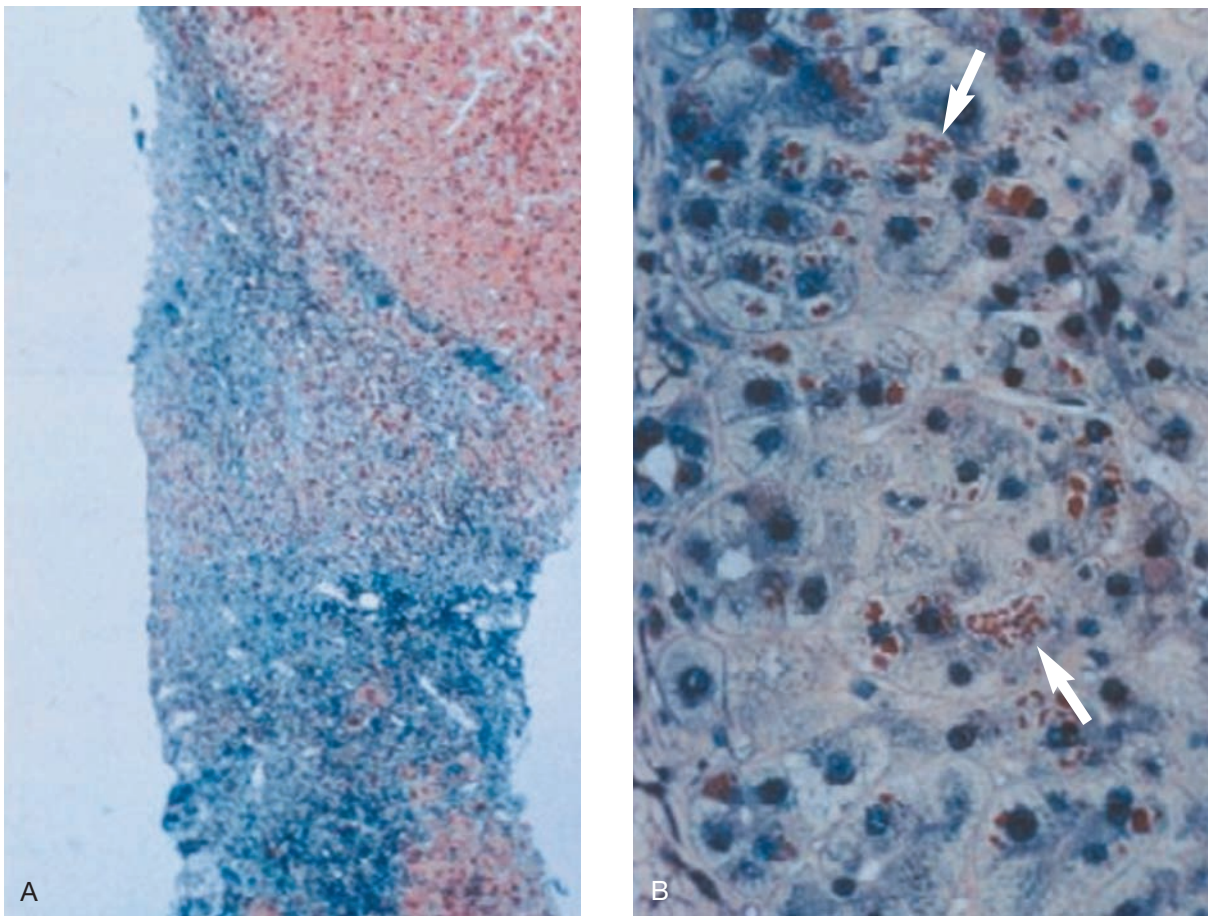

Fig. 6. Histologic features of the liver in α_1-antitrypsin deficiency. Characteristic periodic acid-Schiff–positive diastase-resistant globules (*arrows*) have accumulated in hepatocytes. *A,* Low-power and, *B*, high-power views.

the liver, their absence does not exclude the diagnosis of AAT deficiency. The histologic features of the liver in AAT deficiency are shown in Figure 6.

Treatment

No effective medical treatment is available for the liver manifestations of AAT deficiency. As an attempt to decrease the risk of the development of emphysema, patients should refrain from using tobacco. They also should minimize alcohol consumption. In some cases of lung disease, AAT has been infused, but it is not helpful for liver disease. AAT deficiency 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 was available.

OLT is the only definitive treatment for AAT deficiency. It cures the liver disease because the recipient assumes the Pi phenotype of the donor.

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CHAPTER 29

Cholestatic Liver Disease: Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, and AIDS-Associated Cholangiopathy

Keith D. Lindor, MD

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. Primary sclerosing cholangitis is about half as common as primary biliary cirrhosis. Other cholestatic conditions in adults include autoimmune cholangitis (sometimes known as antimitochondrial antibody [AMA]-negative primary biliary cirrhosis), acquired immunodeficiency syndrome (AIDS)-associated cholangiopathy, and miscellaneous conditions.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for cholestasis in adults without biliary obstruction is listed in Table 1.

Table 1. Differential Diagnosis for Cholestasis in Adults Without Large Duct Biliary Obstruction

Drug-induced cholestasis
Primary biliary cirrhosis
Autoimmune cholangitis
Primary sclerosing cholangitis
Small duct primary sclerosing cholangitis
AIDS-associated cholangiopathy
Idiopathic adulthood ductopenia
Idiopathic biliary ductopenia
Cholestasis of pregnancy
Cystic fibrosis
Sarcoidosis
Granulomatous hepatitis

AIDS, acquired immunodeficiency syndrome.

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 AMAs in 95% of patients. These patients present with biochemical features of cholestasis and may be symptomatic. Fatigue is the most common symptom, but it is nonspecific and not useful in establishing the diagnosis. Pruritus is less common

Abbreviations: AIDS, acquired immunodeficiency syndrome; AMA, antimitochondrial antibody; ERCP, endoscopic retrograde cholangiopancreatography.

but may occur in 30% to 50% of patients. Increasingly, primary biliary cirrhosis is being recognized in asymptomatic patients on the basis of abnormal liver test results. The alkaline phosphatase level is prominently increased, but serum levels of cholesterol and IgM also can be abnormally high. The most characteristic finding is AMAs, which recognize the lipoic acid binding site on an enzyme in the pyruvate dehydrogenase complex. The diagnosis often is established by the finding of high-titer AMA in the appropriate clinical setting. Although liver biopsy helps confirm the diagnosis and provides information about histologic staging, it may not be required 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.

Autoimmune Cholangitis

Autoimmune cholangitis, or *AMA-negative primary biliary cirrhosis*, is characterized by clinical and histologic features identical to those of primary biliary cirrhosis. However, the patients do not have AMAs, but 95% have either antinuclear or antismooth muscle antibodies. Occasionally, these patients are confused with those who have overlapping autoimmune hepatitis and primary biliary cirrhosis, but the histologic features and biochemical profile generally help differentiate autoimmune cholangitis from the overlap between primary biliary cirrhosis and autoimmune hepatitis.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is the next most common cholestatic condition in adults. About 70% of the 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 tends to be younger, around 40 years for primary sclerosing cholangitis compared with 50 years for primary biliary cirrhosis. AMAs rarely are present (≤2% of patients). Liver biopsy can help confirm the 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. Unlike primary biliary cirrhosis, direct cholangiography is necessary to establish the diagnosis of primary sclerosing cholangitis. Occasionally, patients have normal cholangiographic findings, but the histologic and clinical features (history of inflammatory bowel disease) suggest primary sclerosing cholangitis. These patients are considered to have small duct primary sclerosing cholangitis.

AIDS-Associated Cholangiopathy

AIDS-associated cholangiopathy is defined as biliary obstruction due to infections that lead to biliary strictures. This was more common in AIDS patients before highly active retroviral therapy was introduced. The frequency has now decreased. The usual organisms include *Cryptosporidium parvum*, microsporida, 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 counts and may manifest with right upper quadrant pain and diarrhea; fever and jaundice are less common. Alkaline phosphatase levels usually are inceased. 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 one-half of the patients are those of papillary stenosis and sclerosing cholangitis. Patterns of intrahepatic and extrahepatic involvement without papillary stenosis, papillary stenosis alone, or intrahepatic involvement alone are less common.

Often, treatment against the causative agent is ineffective. Treatment with highly active retroviral therapy decreases the percentage of patients with human immunodeficiency virus 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, we prescribe ursodiol at a dose of 13 to 15 mg/kg daily, in divided doses, for patients with

any stage of primary biliary cirrhosis who have abnormal findings on liver tests. Patients who meet minimal listing criteria for liver transplantation should be referred for evaluation, but there is no harm in initiating ursodiol therapy while awaiting a donor organ. Ursodiol therapy should be approached gradually over 2 to 3 weeks to avoid precipitating pruritus, which can occur if the full dose is given initially. Ursodiol improves survival free of transplantation, decreases the risk of the development of cirrhosis and varices, and lowers lipid levels. Prognostic models valid in the absence of therapy remain valid when scores are recalculated after 6 months of therapy and can provide useful information. However, not all patients have a response to ursodiol therapy. Approximately 35% of patients have complete biochemical normalization, with an excellent clinical response. Once ursodiol therapy is begun, it appears to be a lifelong need, and patients should be instructed accordingly. Side effects are minimal.

Autoimmune Cholangitis

Patients with autoimmune cholangitis typically have a response to ursodiol therapy, showing the usual response of patients with primary biliary cirrhosis. Occasionally, these patients have a response to corticosteroids or the combination of ursodiol and corticosteroids. This is particularly likely in patients with overlap of primary biliary cirrhosis and autoimmune hepatitis. Most clinicians would begin treatment with ursodiol alone and add corticosteroids if the results of liver biochemistry tests did not improve after 3 to 6 months.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is the most troublesome of the more common adult cholestatic liver diseases because no effective therapy is available. Ursodiol in standard doses has inconsistent effects. Patients may have evidence of rapidly progressive jaundice, may suddenly develop pruritus, 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 (Fig. 1). Cholangiocarcinoma, a biliary stone in the common bile duct, 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 dilatation of dominant strictures. The role of stenting after dilatation has not been defined clearly.

MANAGEMENT OF COMPLICATIONS OF CHOLESTASIS

Complications of cholestasis require management. Malabsorption and deficiency of fat-soluble vitamins may occur, especially if cholestasis is severe. These patients require periodic monitoring. Levels

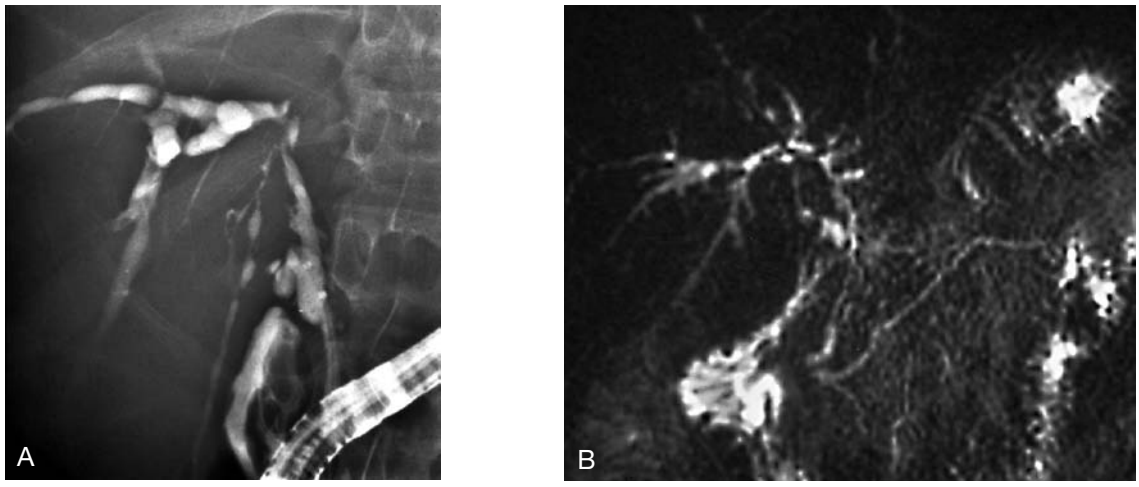

Fig. 1. Comparison of the findings of, *A*, endoscopic retrograde cholangiopancreatography and, *B*, magnetic resonance cholangiography in the same patient with primary sclerosing cholangitis.

of vitamins A, E, and D can be measured in serum directly, and the 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, common in patients with cholestasis, does not appear to be associated frequently with atherosclerosis. We have not been aggressive in prescribing antihyperlipidemic therapy for these patients because some of the agents may be hepatotoxic; instead, we have usually settled for the antihypercholesterolemic effects of ursodiol when given for primary biliary cirrhosis.

Pruritus

Pruritus can be one of the most troublesome symptoms of patients with cholestasis. The severity of the pruritus does not correlate closely with the severity of the underlying liver disease, and pruritus may resolve as the disease progresses. Ursodiol reduces pruritus in some patients with primary biliary cirrhosis, but for those who remain symptomatic, antihistamines (ie, diphenhydramine 25-30 mg by mouth at bedtime) may relieve the pruritus and permit sleep. Cholestyramine (4-g packets 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. Naltrexone (50 mg daily) may be useful for some patients, although there is less experience with this drug than with the others. Liver transplantation 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 fewer than 5% of patients with osteopenic bone disease and cholestasis. Almost all bone disease evaluated in North America in this setting 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. The patients lose bone at a rate 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. The 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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CHAPTER 30

Drug-Induced Liver Injury

John J. Poterucha, MD

Drug-induced liver injury is common in both inpatient and outpatient settings. In one study, the overall incidence of drug-induced liver disease was 13.9 per 100,000 population annually. About 5% to 10% of hospitalizations for jaundice are due to drugs, and medications cause about 50% of cases of fulminant liver failure. Drug-induced liver injury is the most common cause of regulatory action for drugs, including withdrawal from the market. Predisposing factors for drug-induced liver injury are obesity or malnutrition, extremes of age, female sex, pregnancy, polypharmacy, previous drug-induced liver injury, genetic influences, and preexisting liver disease.

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 allow excretion into the bile and urine. The metabolizing systems are divided into phase I and phase II reactions. Phase I reactions involve the cytochrome P-450 (CYP) family of enzymes and include the addition of polar groups by oxidation, reduction, or hydrolysis. The metabolites formed by phase I reactions may be toxic if not subsequently excreted or further metabolized. Activity of phase I reactions is influenced by age, other drugs, and toxins (Table 1). The CYP3A subfamily is the most prominent P-450 system involved in drug metabolism.

Phase II 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 II reactions may affect the parent compound directly (ie, without a previous phase I reaction). Age, dietary factors, and nutritional status can alter the activity of phase II reactions. The influence of alterations in drug-metabolizing systems on drug-induced liver injury is incompletely understood.

MECHANISMS OF DRUG-INDUCED LIVER INJURY

Drug-induced liver injury can be divided broadly into direct chemical toxicity and idiosyncratic reactions. *Direct toxicity* is dose related; the most common example is the hepatotoxicity associated

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP, cytochrome P-450; HIV, human immunodeficiency virus.

Table 1. Drugs and Conditions That Affect Activity of the Cytochrome P-450 (CYP) System

Inhibit CYP activity	Induce CYP activity
Clarithromycin	Carbamazepine
Erythromycin	Chronic alcohol use
Fluconazole	Phenobarbital
Increasing age	Phenytoin
Itraconazole	Rifampin
Ketoconazole	
Ritonavir	

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.

Idiosyncratic reactions, which are unpredictable and unrelated to medication dose, can be due to either metabolic factors or hypersensitivity. Most drug-induced hepatotoxicity is metabolic, which involves the accumulation of toxic metabolites within hepatocytes that leads to necrosis and inflammation. Although genetic influences in metabolic drug-induced liver injury are probably important, they are incompletely understood. An example of a predictable metabolic drug injury occurs with irinotecan toxicity in patients with Gilbert's syndrome, because the metabolism of irinotecan is impaired by a deficiency in the same enzyme that contributes to the conjugation of bilirubin.

Liver injury from hypersensitivity usually follows 1 to 5 weeks of exposure to the drug and is accompanied by rash, fever, and eosinophilia and recurs with rechallenge. Although the features of hypersensitivity are very suggestive of drug-induced liver injury, hypersensitivity features are seen in only about 20% of all cases of idiosyncratic drug-induced liver injury. Examples of drugs that can result in a hypersensitivity reaction are sulfonamides, amoxicillin-clavulanate, phenytoin, and halothane.

Because the specific mechanism of drug-induced liver injury is not understood in most cases, predicting this injury usually is not possible. Deficiencies in certain P-450 enzymes, genetic polymorphisms in immune processes of certain interleukins, and certain human leukocyte antigen haplotypes have all been associated with drug-induced liver injury. Perhaps in the future, pharmacogenetic testing will permit the prediction of individual patterns of drug metabolism and assessment of risk factors for drug-induced liver injury, thus allowing avoidance of the agent by susceptible persons.

DIAGNOSIS

There is no specific test for drug-induced liver injury. The maxim that "almost any drug can do 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 drug-induced liver injury occurs within a year after treatment is started with the drug. Drug-induced liver injury should be suspected when liver injury occurs soon after the initiation of treatment with the agent 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 drug-induced liver injury is made. A recent report that showed a positive test for hepatitis E (despite an absence of relevant travel history) in patients previously thought to have drug-induced liver injury emphasizes the difficulty with diagnosis. Resolution of the injury after withdrawal of treatment with the drug is supportive of the diagnosis of drug-induced liver injury, although the timing of improvement after the withdrawal varies. Also, improvement after withdrawal of the agent may be coincidental if the liver injury is due to an identified cause that coincidentally improves as the drug is withdrawn.

Hepatotoxicity due to drugs can be categorized by the biochemical pattern of liver injury according to the following equation:

$$R = \frac{\text{ALT (measured in multiples of ULN)}}{\text{ALP (measured in multiples of ULN)}}$$

where ALP is alkaline phosphatase, ALT is alanine aminotransferase, and ULN is upper limit of normal. Hepatotoxicity is considered hepatocellular when R is more than 5, cholestatic when R is less than 2, and mixed when R is between 2 and 5. Although most drugs have a signature pattern of hepatotoxicity (Table 2), different biochemical presentations of drug-induced liver injury can occur with the same agent.

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 the agent. For example, isoniazid increases the ALT level more than 3 times the upper limit of normal in 15% of patients, but the enzyme levels usually normalize despite continued treatment. Generally, there should be concern about clinically significant drug-induced liver injury when liver enzyme levels increase more than 5 times the upper limit of normal or when impaired liver function is noted.

Table 2. Patterns of Liver Injury for Certain Drugs

Hepatocellular (elevated ALT)	Mixed (elevated ALP + elevated ALT)	Cholestatic (elevated ALP)
Acarbose	Amitriptyline	Amoxicillin-clavulanic acid
Acetaminophen	Azathioprine	Anabolic steroids
Allopurinol	Captopril	Chlorpromazine
Amiodarone	Carbamazepine	Clopidogrel
Baclofen	Clindamycin	Oral contraceptives
Buproprion	Cyproheptadine	Erythromycins
Fluoxetine	Enalapril	Estrogens
HAART drugs	Flutamide	Irbesartan
Herbals: kava kava and germander	Nitrofurantoin	Mirtazapine
Isoniazid	Phenobarbital	Phenothiazines
Ketoconazole	Phenytoin	Terbinafine
Lisinopril	Sulfonamides	Tricyclics
Losartan	Trazodone	
Methotrexate	Trimethoprim-sulfamethoxazole	
NSAIDs	Verapamil	
Omeprazole		
Paroxetine		
Pyrazinamide		
Rifampin		
Risperidone		
Sertraline		
Statins		
Tetracyclines		
Trazodone		
Trovafloxacin		
Valproic acid		

ALP, alkaline phosphatase; ALT, alanine aminotransferase; HAART, highly active antiretroviral therapy; NSAID, nonsteroidal antiinflammatory drug.

From Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006;354:731-9. Used with permission.

HISTOLOGIC PATTERNS OF DRUG-INDUCED LIVER INJURY

Histologic features of centrilobular necrosis, eosinophilic infiltration, and granulomas are suggestive of drug-induced liver injury. However, these findings are not specific for diagnosis, and clinical correlation is mandatory. Drug-induced liver injury may mimic other liver diseases and should be part of the differential diagnosis of the multiple histologic patterns.

Steatosis

Drug-induced liver injury should be considered in patients with hepatic steatosis. Valproic acid and tetracycline cause acute development of microvesicular steatosis, whereas tamoxifen, amiodarone, methotrexate, and corticosteroids cause steatosis that develops over months and is predominantly macrovesicular. More recently, the chemotherapeutic agents irinotecan and oxaliplatin have been associated with the development of steatohepatitis. Chronic liver injury from methotrexate and amiodarone can lead even to the development of advanced fibrosis.

Portal and Periportal Hepatitis

Certain drugs produce protein adducts that can act as neoantigens, producing clinical features that mimic those of autoimmune hepatitis. The most common offenders are minocycline and nitrofurantoin. Drug-induced autoimmune hepatitis is associated with more than 6 months of exposure to the drug, female sex, and the presence of HLA types DR3 and DR4. This type of drug-induced liver injury does not always remit spontaneously after the drug has been withdrawn, and treatment with corticosteroids has produced variable results. A histologic pattern that mimics that of primary biliary cirrhosis can develop after the administration of chlorpromazine.

Sinusoidal Obstruction Syndrome

The sinusoidal obstruction syndrome, or veno-occlusive disease, is due most often to myeloablative therapy that is given before stem cell transplantation, but it can occur also after the administration of azathioprine. The presentation is similar to that of Budd-Chiari syndrome, with ascites present in nearly all patients. Anticoagulation can be considered for treatment of sinusoidal obstruction syndrome, although the mortality rate is high, especially after bone marrow transplantation, in which 15% to 30% of patients die.

EXAMPLES OF DRUG-INDUCED LIVER INJURY

Acetaminophen

Most drug-induced liver injury is acute. Drugs commonly implicated in acute hepatitis are acetaminophen, antituberculosis agents, antibiotics, and antiseizure drugs. The most common cause of fulminant liver failure in the United States and Europe is acetaminophen toxicity. The metabolism of acetaminophen is shown in Figure 1. Decreases in glutathione found 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.

Adding to the role of acetaminophen in fulminant liver failure, acetaminophen adducts (*N*-acetyl-*p*-quinoneimine bound to protein) have been identified in 20% of cases of "indeterminate" fulminate liver failure. More than half of these cases have been "therapeutic misadventures," in which patients inadvertently ingested toxic doses of acetaminophen. Many of these patients have chronic alcoholism, which up-regulates the production of the toxic metabolites of acetaminophen.

Acetaminophen hepatotoxicity is characterized by very high levels of aminotransferases, often more than 5,000 IU/mL. Renal failure is also common. The degree of increase in the aspartate aminotransferase (AST) level at the time of presentation following an acetaminophen overdose is helpful in predicting hepatotoxicity. Patients with AST levels less than 50 IU/mL at presentation rarely develop hepatotoxicity, whereas 16% of those with AST levels more than 1,000 IU/mL at presentation die or need liver transplantation. Patients with acetaminophen hepatotoxicity and poor prognostic markers should be hospitalized and their condition monitored. The criteria for liver transplantation are listed in Table 6 in Chapter 21. 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*-quinoneimine. 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 given up to 24 hours after ingestion because of its putative hepatoprotective effects.

Antibiotics

Antibiotics are the drug class that most commonly causes nonfulminant liver injury. 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. This delayed phenomenon makes diagnosis difficult. Toxicity may be hepatocellular or cholestatic. Similar to other forms of drug-induced cholestatic liver injury, the cholestasis due to amoxicillin-clavulanic acid may take weeks to resolve and may even result in chronic liver injury. Telithromycin is a ketolide antibiotic that recently has been reported to cause severe hepatotoxicity.

Antiretroviral Agents

Drugs against the human immunodeficiency virus (HIV) cause hepatotoxicity in 2% to 18% of patients. Drug-induced liver injury may be difficult to diagnose in these patients because most of them take multiple drugs and may have other risk factors for liver disease, such as viral hepatitis or alcoholism. Drug-induced liver injury may be more common in patients with viral hepatitis, especially hepatitis C. All classes of antiretroviral therapy can produce liver injury. Of the protease inhibitors, ritonavir, especially at high dose, has 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.

The major toxic effect of nucleoside reverse transcriptase inhibitors is lactic acidosis. An asymptomatic increase in lactate level without metabolic acidosis occurs in 8% to 18% of patients and may be transient. Lactic acidosis syndrome is likely due to mitochondrial toxicity and may be accompanied by severe liver dysfunction. 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. Ribavirin for hepatitis C in patients taking zidovudine is associated with an increased risk of anemia.

A hypersensitivity reaction due to the nonnucleoside reverse transcriptase inhibitor nevirapine occurs in 2.3% of patients. This develops within a few weeks after the start of therapy and may include hepatotoxicity. Even more common, late-onset toxicity may also occur. Patients who have chronic viral hepatitis are likely at increased risk for toxicity with nevirapine therapy.

Herbal Therapies

Herbal medications always should be considered in the differential diagnosis of liver injury. Many patients do not consider over-the-counter, nutritional, or herbal supplements as "medicines;" 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 drug-induced liver injury is difficult because mild increases in liver enzyme levels are common within 1 month after the initiation of statin therapy, but the levels nearly always improve despite continued administration of these agents. Furthermore, mildly fluctuating liver enzyme levels are seen 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

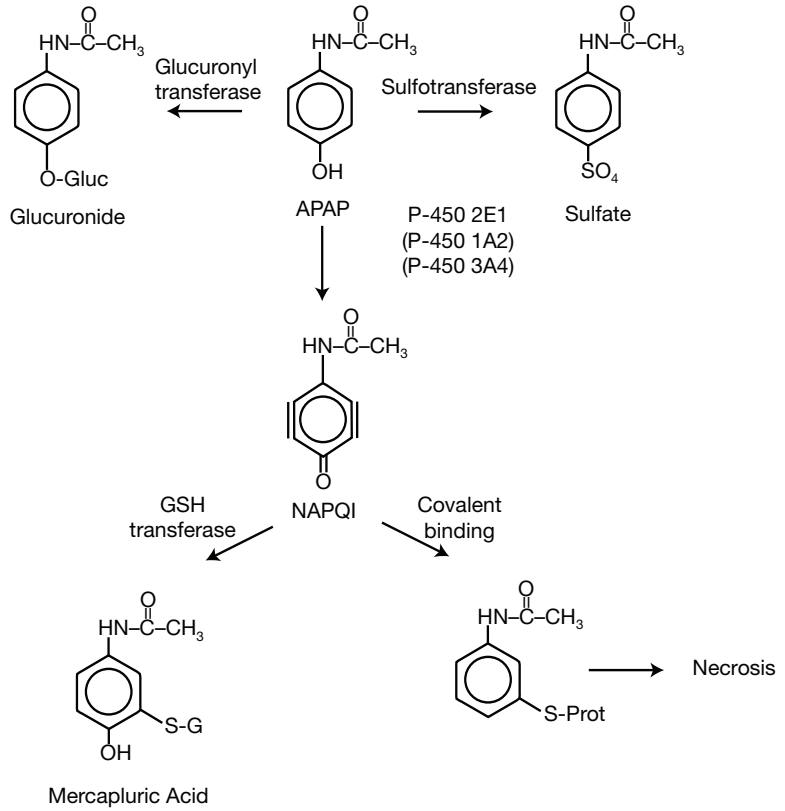

Fig. 1. Metabolism of acetaminophen. Most APAP is conjugated to either glucuronide or sulfate. That portion which is oxidized to NAPQI is further detoxified by glutathione transferase. If this system is overwhelmed, NAPQI binds to cellular targets leading to hepatocellular necrosis. APAP, acetaminophen; GSH, glutathione; NAPQI, *N*-acetyl-*p*-benzoquinoneimine. (From Zimmerman HJ. Acetaminophen hepatotoxicity. Clin Liver Dis. 1998;2:527. Used with permission.)

the issue, although it has been well demonstrated that statin drugs are safe for patients with nonalcoholic fatty liver disease. In fact, small studies have shown histologic improvement in these patients.

Serious toxicity from statin agents is rare. The risk of fulminant 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, a value that is similar to the rate of idiopathic fulminant liver failure. 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. Nevertheless, monitoring is still recommended, usually before treatment is initiated and 12 weeks after therapy is initiated. Monitoring should be considered also after a change in dose or the administration of a second lipid-lowering agent. 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 elevated liver enzyme levels and, when used in combination with statins, may rarely cause clinically significant hepatoxicity. Sustained-release niacin also may produce symptomatic hepatotoxicity.

TREATMENT AND PROGNOSIS OF DRUG-INDUCED LIVER INJURY

For most cases of drug-induced liver injury, treatment is withdrawal of the agent and general support. Patients with severe liver dysfunction who are potential candidates for liver transplantation should be referred to a transplant center. For acetaminophen

toxicity, *N*-acetylcysteine should be given. Carnitine may be helpful for valproic acid-induced microvesicular steatosis. Drug-induced autoimmune hepatitis that does not improve spontaneously can be treated with corticosteroids.

The prognosis of drug-induced acute hepatitis varies. According to Hy's rule (named after the hepatologist Hyman Zimmerman), patients with jaundice due to drug-induced hepatocellular injury have a 10% mortality rate without transplantation, even if treatment with the drug is discontinued promptly. Patients with fulminant liver failure due to idiosyncratic drug injury have an 80% mortality rate without transplantation. The histologic features of drug-induced hepatitis include diffuse lobular injury that may be most prominent in zone 3 (centrilobular area). The presence of eosinophils is very suggestive of drug-induced liver injury, but it is not a sensitive marker.

Cholestatic liver injury can mimic large bile duct obstruction both clinically and histologically. Cholestatic liver injury is less likely to be serious than hepatocellular drug injury but is more likely to be prolonged. In addition to the clinical features of increased alkaline phosphatase levels and, frequently, jaundice, cholestatic drug-induced liver injury often has a more gradual improvement than that of drug-induced hepatocellular injury. The mechanism of drug-induced cholestasis is not well known, but it may involve injury to bile acid transporters. 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.

RECOMMENDED READING

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CHAPTER 31

Autoimmune Hepatitis

Albert J. Czaja, MD

DIAGNOSIS

Autoimmune hepatitis is a self-perpetuating inflammation of the liver of unknown cause that is associated with interface hepatitis seen on histologic examination, hypergammaglobulinemia, and autoantibodies. An international panel has codified the diagnostic criteria, and definite diagnosis requires the exclusion of hereditary (Wilson's disease, genetic hemochromatosis, and α_1-antitrypsin deficiency), viral (hepatitis A, B, and C virus infections), and drug-induced (diclofenac, isoniazid, propylthiouracil, α-methyldopa, minocycline, or nitrofurantoin-related) conditions (Table 1).

The 6-month requirement to establish chronicity has been waived, and an acute, rarely fulminant, presentation has been recognized that may resemble acute viral or toxic hepatitis. A cholestatic form of autoimmune hepatitis is not recognized, and a marked increase (more than twofold the upper limit of normal) 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 who have cryptogenic chronic hepatitis.

Interface hepatitis is the histologic hallmark of autoimmune hepatitis (Fig. 1). The morphologic pattern is nonspecific and occurs in acute and chronic liver disease 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 (Fig. 2). A lobular, or panacinar, hepatitis frequently accompanies interface hepatitis (Fig. 3), and a centrilobular (zone 3) necrosis has also been described (Fig. 4). 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

Abbreviations: AIRE, autoimmune regulator; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; anti-ASGPR, asialoglycoprotein receptor antibodies; anti-LC1, liver cytosol type 1 antibodies; anti-LKM1, liver/kidney microsome type 1 antibodies; anti-SLA/LP, soluble liver antigen/liver pancreas antibodies; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; AST, aspartate aminotransferase; HCV, hepatitis C virus; IL, interleukin; pANCA, perinuclear antineutrophil cytoplasmic antibodies; SMA, smooth muscle antibodies.

Table 1. Criteria for Diagnosis of Autoimmune Hepatitis (AIH)

Diagnostic criteria	
Definite AIH	**Probable AIH**
Normal AAT phenotype	Partial AAT deficiency
Normal ceruloplasmin level	Abnormal copper or ceruloplasmin level but Wilson's disease excluded
Normal iron and ferritin levels	Nonspecific iron or ferritin abnormalities
No active hepatitis A, B, or C infection	No active hepatitis A, B, or C infection
Daily alcohol <25 g	Daily alcohol <50 g
No recent hepatotoxic drugs	No recent hepatotoxic drugs
Predominant serum aminotransferase abnormality	Predominant serum aminotransferase abnormality
Globulin, γ-globulin, or IgG level ≥1.5 times normal	Hypergammaglobulinemia of any degree
ANA, SMA, or anti-LKM1 ≥1:80 in adults and ≥1:20 in children; no AMA	ANA, SMA, or anti-LKM1 ≥1:40 in adults; other autoantibodies
Interface hepatitis—moderate to severe	Interface hepatitis—moderate to severe
No biliary lesions, granulomas, or prominent changes suggestive of another disease	No biliary lesions, granulomas, or prominent changes suggestive of another disease

AAT, α_1-antitrypsin; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; anti-LKM1, antibodies to liver/kidney microsome type 1; IgG, serum immunoglobulin G level; SMA, smooth muscle antibodies.

Modified from Czaja AJ. Autoimmune liver disease. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. Vol 2. 4th ed. Philadelphia: Saunders; 2003. p. 1163-1202. Used with permission.

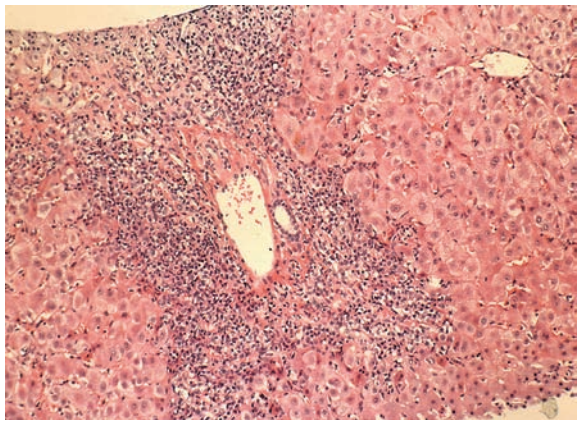

Fig. 1. Interface hepatitis. The limiting plate of the portal tract is disrupted by an inflammatory infiltrate that extends into the acinus. Interface hepatitis is a requisite for the diagnosis of autoimmune hepatitis, but it is not specific for the diagnosis. (Hematoxylin and eosin; ×200.) (From Czaja AJ. Current concepts in autoimmune hepatitis. Ann Hepatol. 2005;4:6-24. Used with permission.)

(Table 2). 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.

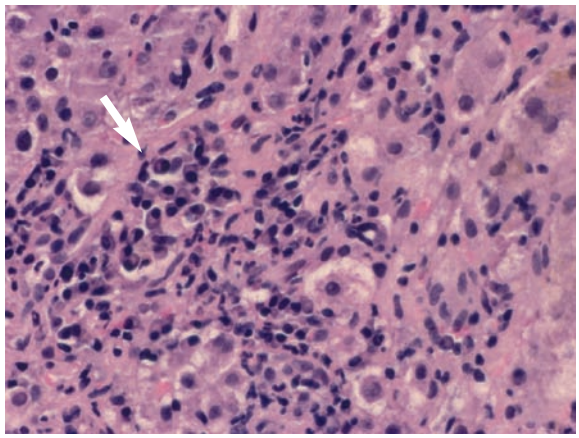

Fig. 2. Plasma cell infiltration of the hepatic parenchyma. Plasma cells (*arrow*) are characterized by a cytoplasmic halo adjacent to a deeply basophilic nucleus. Plasma cells typically are abundant at the interface and throughout the acinus, but they do not have diagnostic specificity. (Hematoxylin and eosin; ×400.) (From Czaja AJ. Current concepts in autoimmune hepatitis. Ann Hepatol. 2005;4:6-24. Used with permission.)

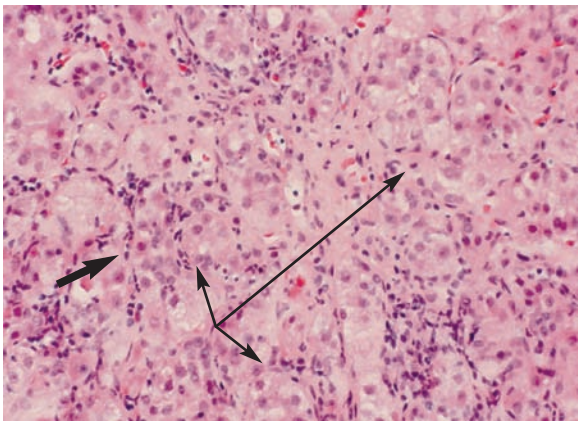

Fig. 3. Panacinar hepatitis. Cellular infiltrates (*thick arrow*) line sinusoidal spaces in association with liver cell degenerative and regenerative changes. Rosettes of hematocytes (*thin arrows*) are also present. (Hematoxylin and eosin; ×200.)

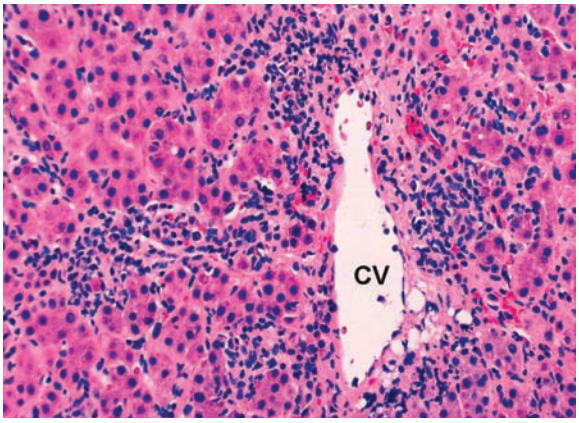

Fig. 4. Centrilobular (Rappaport zone 3) necrosis. Inflammatory cells and injured hepatocytes are distributed mainly in the centrilobular zone 3 (*CV*) area. (Hematoxylin and eosin; ×200.) (From Czaja AJ, Carpenter HA. Autoimmune hepatitis. In: Burt AD, Portmann BC, Ferrell LD, editors. MacSween's pathology of the liver. 5th ed. London: Churchill Livingstone; 2007. p. 493-515. Used with permission.)

FREQUENCY AND ETHNIC DISTRIBUTION

Autoimmune hepatitis afflicts 100,000 to 200,000 persons in the United States and accounts for 5.9% of liver transplantations performed in the United States. Among white northern Europeans, its mean annual incidence is 1.9 per 100,000, and its point prevalence is 16.9 per 100,000. Its occurrence is similar to that of primary biliary cirrhosis and primary sclerosing cholangitis and less than that of chronic viral hepatitis and alcoholic liver disease. Autoimmune hepatitis occurs mainly 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, the occurrence of autoimmune hepatitis is now recognized to be worldwide. Ethnic background may affect its clinical presentation, and 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; Asians 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, and measles viruses) and drugs (diclofenac, isoniazid, α-methyldopa, minocycline, nitrofurantoin, and propylthiouracil). Hepatitis A virus infection and minocycline have been implicated most often worldwide. 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. A long lag time between antigenic exposure and disease expression and the persistence of disease after the disappearance of the triggering event further complicate efforts to identify an etiologic basis. The target autoantigen responsible for autoimmune hepatitis may have a short epitope that commonly

Table 2. Revised Scoring System of the International Autoimmune Hepatitis Group for the Diagnosis of Autoimmune Hepatitis*

Factors	Score	Factors	Score
Female sex	+2	Hepatotoxic drugs	
ALP:AST (ALT) ratio		Yes	–4
>3	–2	No	+1
<1.5	+2	Alcohol use	
γ-Globulin or IgG levels		<25 g/day	+2
>2 ULN	+3	>60 g/day	–2
1.5-2 ULN	+2	HLA-DR3 or HLA-DR4	+1
1-1.4 ULN	+1	Concurrent immune disease	+2
ANA, SMA, or anti-LKM1		Other liver-related autoantibody	+2
>1:80	+3	Interface hepatitis	+3
1:80	+2	Plasmacytic infiltrate	+1
1:40	+1	Rosettes	+1
<1:40	0	No characteristic features	–5
AMA	–4	Biliary changes	–3
Viral markers		Other features (fat, granulomas)	–3
Seropositive	–3	Treatment response	
Seronegative	+3	Complete	+2
		Relapse	+3

ALP:AST, ratio of serum alkaline phosphatase to aspartate aminotransferase level; ALT, serum alanine aminotransferase level; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; anti-LKM1, antibodies to liver/kidney microsome type 1; HLA, human leukocyte antigen; SMA, smooth muscle antibodies; ULN, upper limit of normal.

**Pretreatment score: definite diagnosis, >15; probable diagnosis, 10-15. Posttreatment score: definite diagnosis, >17; probable diagnosis, 12-17.*

Modified from Czaja AJ: Autoimmune hepatitis. In: Feldman M, Friedman LS, Sleisenger MH, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Vol 2. 7th ed. Philadelphia: Saunders; 2002. p. 1462-73. Used with permission.

is shared by other peptides within the patient. Repeated exposures to the triggering antigen, in turn, may trigger autoreactive responses against the liver and anatomically distant organs, thereby causing not only autoimmune hepatitis but concurrent immune diseases.

CLINICAL FEATURES

Women constitute at least 70% of cases, and 50% are younger than 40 years (Table 3). Onset is usually between the third and fifth decades, but the age at onset may range from infancy to the extreme elderly. Autoimmune hepatitis tends to be more severe in children than in adults. Children commonly have cirrhosis at 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.

Elderly patients more commonly have cirrhosis at presentation and concurrent thyroid (Graves' disease or autoimmune thyroiditis) or rheumatic (rheumatoid arthritis, Sjögren's syndrome, or

Table 3. Typical Features of Autoimmune Hepatitis

Feature	Patients, %
Clinical features	
Female sex	70
Younger than 40 years	50
Acute onset	40
Asymptomatic	25-34
Common symptoms	
Fatigue	85
Arthralgia	30
Myalgia	30
Develop later from asymptomatic presentation	26-70
Frequent physical findings	
Normal	80
Hepatomegaly	20
Typical laboratory findings	
Increased serum levels of AST and ALT	100
Increased serum levels of γ-globulin and IgG	90
Mild hyperbilirubinemia (bilirubin <3 mg/dL)	83
Serum alkaline phosphatase increased <2-fold ULN	67
ANA, SMA, or anti-LKM1	87

ALT, alanine aminotransferase; ANA, antinuclear antibodies; anti-LKM1, antibodies to liver/kidney microsome type 1; AST, aspatate aminotransferase; SMA, smooth muscle antibodies; ULN, upper limit of normal.

systemic lupus erythematosus) disorders than young adult patients. Elderly white patients from North America or northern Europe have HLA-DRB1*04 more often and HLA-DRB1*03 less frequently than young adult patients with a similar ethnic background, and they respond well to corticosteroid therapy. These findings suggest that elderly patients have triggering events that are different from those of young adults or that their genetic phenotype is associated with a less vigorous immune response. Aging alters immune responsiveness (immunosenescence) by decreasing the expression of HLA class II molecules and reducing stimulation and proliferation of antigen-stimulated T cells. These effects may attenuate the pathogenic mechanisms in the elderly and render these patients more responsive to treatment.

Forty percent of patients have an abrupt onset of symptoms, 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, including hypergammaglobulinemia and fibrosis or cirrhosis seen on histologic examination, are common in these patients. 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 presentations 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%), 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 myalgia, arthralgia, 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.

Familial occurrences are rare, but autoimmune hepatitis has been reported in siblings, parents, and grandparents of afflicted persons. First-degree relatives may have abnormal serum levels of immunoglobulin (47%), autoantibodies (42%), and hypergammaglobulinemia (34%). In one series, 3 of 55 families (5%) had more than one family member with chronic liver disease. The rarity of familial clustering, the uncertain pathogenesis of the disease, and the variable phenotype of the illness do not justify family screening.

PHYSICAL FINDINGS

Most patients with autoimmune hepatitis have normal physical examination findings despite severe inflammatory activity (Table 3). 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. Hyperpigmentation and xanthelasmas are incompatible with the diagnosis. 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 3). The serum γ-globulin level is typically, but not invariably, increased, and the diagnosis is suspect without this finding. 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. A polyclonal increase in serum immunoglobulin concentrations is typical, and the IgG fraction predominates.

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 twofold the upper limit of normal in only 33% and more than fourfold the upper limit of normal in only 10%.

Antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and anti-LKM1 are the conventional serologic markers of autoimmune hepatitis. None is pathogenic or has prognostic value, and they may not be present in all patients with the disease. Many patients who are seronegative for the conventional autoantibodies subsequently have these autoantibodies, as shown with repeated testing during the course of the illness and its treatment. Other patients may have serologic reactivities that are outside the standard repertoire or are still undiscovered.

HLA-DRB1*03, HLA-DRB1*04, and HLA-DRB1*03–DRB1*04 are the principal risk factors for autoimmune hepatitis in white North American and northern European patients, and they are found in 85% of cases (Table 4). HLA-DRB1*13 is found mainly in South American children. HLA-DRB1*07 and DQB1*02 are the risk factors associated with the disease characterized by anti-LKM1. HLA-DRB1*03 is associated with early-age onset, diminished response to corticosteroids, and frequent requirement for liver transplantation. 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.

CONCURRENT IMMUNE DISEASES

Concurrent immune diseases are present in 30% to 48% of patients with autoimmune hepatitis (Table 5). Adults have mainly autoimmune thyroiditis, Graves' disease, ulcerative colitis, or synovitis, and children have mainly vitiligo, insulin-dependent diabetes mellitus, or autoimmune sclerosing cholangitis. Elderly patients (>60 years) frequently have autoimmune thyroiditis or rheumatic conditions (eg, rheumatoid arthritis or Sjögren's syndrome). Celiac sprue may be asymptomatic and present in 3% of patients; multiple immune diseases occur in 6% of patients. Ulcerative colitis suggests the possibility of primary sclerosing cholangitis, and it justifies the performance of cholangiography. Of the patients who have autoimmune hepatitis and ulcerative colitis, 59% have normal cholangiograms and respond well to corticosteroid treatment. The

Table 4. Genetic Predispositions for Autoimmune Hepatitis

Genetic risk factor	Pertinence	Associations
HLA-DRB1*03	Principal risk factor in white North Americans and northern Europeans	Type 1 autoimmune hepatitis Young age at onset Treatment failure is more common Liver transplant is more frequent
HLA-DRB1*04	Secondary and independent risk factor in white North Americans and northern Europeans	Type 1 autoimmune hepatitis Older patients Women Frequent immune diseases Good response to treatment
*DRB1*0301*	Principal susceptibility allele in white North Americans and northern Europeans	Pertienent allelic component of HLA-DRB1*03 responsible for disease effects
*DRB1*0401*	Secondary susceptibility allele in white North Americans and northern Europeans	Pertinent allelic component of HLA-DRB1*04 responsible for disease effects
HLA-DRB1*07	Susceptibility factor in type 2 autoimmune hepatitis	Associated with anti-LKM1 in autoimmune hepatitis and chronic hepatitis C
*DRB1*1301*	Principal susceptibility allele in South America (Brazil and Argentina)	Type 1 autoimmune hepatitis Mainly in children Favors protracted hepatitis A infection
*DRB1*1501*	Protective allele in white northern Europeans	Low frequency of type 1 autoimmune hepatitis
*DQB1*02*	Susceptibility factor in type 2 autoimmune hepatitis	May be responsibile for type 2 disease and not anti-LKM1

Anti-LKM1, antibodies to liver kidney microsome type 1; HLA, human leukocyte antigen.

other 41% have primary sclerosing cholangitis and are refractory to corticosteroid treatment.

Autoimmune hepatitis is present in 15% of patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). This syndrome is characterized by ectodermal dysplasia, mucocutaneous candidiasis, and multiple endocrine organ failure (parathyroid, ovarian, and adrenal failure). A single gene defect on chromosome band 21q22.3 has been identified as the basis for the syndrome, and the disease is inherited in mendelian fashion. The *APECED* gene encodes for a transcription factor called the *autoimmune regulator* (AIRE), which modulates clonal deletion of autoreactive T cells. APECED does not have HLA-DR associations or female predominance.

AUTOANTIBODIES

ANA, SMA, and anti-LKM1 are the serologic markers of autoimmune hepatitis, and they should be measured in all patients with suspected disease (Table 6). They are not pathogenic, and their behavior does not have important clinical implications. Serum titers do not have prognostic significance, and low titers should not dissuade the diagnosis if other features implicate the disorder. The conventional autoantibodies may be absent in some patients at presentation; serum titers can fluctuate during the course of illness; and the autoantibodies at presentation may not be the same ones expressed later. As floating variables, the major clinical value of autoantibodies is to support the diagnosis.

Table 5. Immune Diseases Associated With Autoimmune Hepatitis

Autoimmune sclerosing cholangitis*	Intestinal villous atrophy
Autoimmune thyroiditis†	Iritis
Celiac disease	Lichen planus
Coomb's-positive hemolytic anemia	Myasthenia gravis
Cryoglobulinemia	Neutropenia
Dermatitis herpetiformis	Pericarditis
Erythema nodosum	Peripheral neuropathy
Fibrosing alveolitis	Pernicious anemia
Focal myositis	Pleuritis
Gingivitis	Pyoderma gangrenosum
Glomerulonephritis	Rheumatoid arthritis†
Graves' disease†	Sjögren's syndrome
Idiopathic thrombocytopenic purpura	Synovitis†
Insulin-dependent diabetes*	Systemic lupus erythematosus
	Ulcerative colitis†
	Urticaria
	Vitiligo*

Mainly in children.

†*Most common associations.*

Modified from Czaja AJ. Autoimmune liver disease. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. Vol 2. 4th ed. Philadelphia: Saunders; 2003. p. 1163-1202. Used with permission.

Other autoantibodies that support the diagnosis of autoimmune hepatitis and whose assay generally is available are perinuclear antineutrophil cytoplasmic antibodies (pANCA), which occur 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 antibodies to tissue transglutaminase or endomysium are useful for excluding the liver disease associated with celiac disease.

Antibodies that promise to enhance diagnostic and prognostic value but which have not been incorporated into a conventional diagnostic algorithm (nonstandard antibodies) are antibodies to actin (anti-actin), soluble liver antigen/liver pancreas (anti-SLA/LP), asialoglycoprotein receptor (anti-ASGPR), chromatin, and liver cytosol type 1 (anti-LC1) (Table 6). Anti-ASGPR, anti-chromatin, and anti-SLA/LP are associated with relapse after treatment withdrawal, and anti-actin and anti-LC1 identify young patients who have aggressive disease. The nonstandard antibodies may emerge as prognostic markers. Anti-SLA/LP have the most promise in this regard because they identify patients who have disease relapse after withdrawal of corticosteroid therapy, have severe disease activity, and possess HLA-DRB1*03.

Cryptogenic chronic hepatitis may be reclassified as autoimmune hepatitis by repeat testing for the conventional autoantibodies or testing for the nonstandard markers (pANCA or anti-SLA/LP). Conventional autoantibodies that are absent at presentation may be expressed later during the course of the disease. Anti-SLA/LP may be present in 18% of patients who are seronegative by the conventional battery, and pANCA may also support the diagnosis in otherwise seronegative patients. Determination of IgA antibodies to tissue transglutaminase or endomysium may indicate celiac disease in patients with cryptogenic disease.

Antimitochondrial antibodies (AMA), including those against the M2 antigens associated with primary biliary cirrhosis, occur 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 have not been associated with a cholestatic clinical syndrome, heralded the emergence of a different disease, or affected treatment response.

The typical autoantibodies of autoimmune hepatitis also can occur in chronic hepatitis B and C. They are usually low titer, background reactivities that should not alter diagnosis or management. Anti-LKM1 have been found in as many as 10% of European patients with chronic hepatitis C. These antibodies are different from the anti-LKM1 found in classic autoimmune hepatitis. Homologies have been described between the antigenic target of anti-LKM1 and the genome of the hepatitis C virus

(HCV), and this molecular mimicry may result in cross-reacting antibodies in some patients. ANA and SMA can occur in acute and chronic hepatitis of diverse causes, including alcoholic and nonalcoholic fatty liver disease. Autoantibodies, regardless of titer or type, expand the differential diagnosis, but they never establish the true nature of the disease.

SUBCLASSIFICATIONS

Two types of autoimmune hepatitis have been proposed on the basis of serologic markers (Table 7). 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.

Type 1 Autoimmune Hepatitis

Type 1 autoimmune hepatitis is characterized by the presence of ANA and SMA (Table 7). It is the most common form of the disease worldwide, especially in white Northern Europeans and North Americans. Seventy percent of the patients are women younger than 40 years, and more than 30%

Table 6. Autoantibodies Associated With Autoimmune Hepatitis (AIH)

Autoantibody	Target	Clinical value
Standard repertoire		
Antinuclear antibodies	Centromere Ribonucleoproteins	Diagnosis of type 1 AIH
Smooth muscle antibodies	Actin, tubulin, vimentin, desmin, skeletin	Diagnosis of type 1 AIH
Anti-LKM1	CYP2D6	Diagnosis of type 2 AIH
Supplemental repertoire		
pANCA	Possible nuclear membrane lamina	Diagnosis of type 1 AIH Reclassification of cryptogenic hepatitis
IgA antibodies to tissue transglutaminase	Recombinant or red blood cell-derived tissue transglutaminase	Celiac disease and cryptogenic hepatitis
IgA endomysial antibody	Endomysium from monkey esophagus or human umbilical cord	Celiac disease and cryptogenic hepatitis
Investigational repertoire		
Antibodies to actin	Microfilaments	Diagnosis of type 1 AIH
Anti-SLA/LP	Cytosolic transfer Ribonucleoprotein complex	Relapse and DRB1*03 Reclassification of cryptogenic hepatitis
Anti-ASGPR	Asialoglycoprotein receptor	Histologic activity and relapse
Antibodies to chromatin	Octomeric chromatin molecule	ANA-positive disease Relapse
Anti-LC1	Formiminotransferase cyclodeaminase	Diagnosis of type 2 AIH Prognostic value

ANA, antinuclear antibodies; anti-ASGPR, antibodies to asialoglycoprotein receptor; anti-LC1, antibodies to liver cytosol type 1; anti-LKM1, antibodies to liver/kidney microsome type 1; anti-SLA/LP, antibodies to soluble liver antigen/liver-pancreas; CYP2D6, cytochrome monooxygenase 206; pANCA, perinuclear antineutrophil cytoplasmic antibodies.

Table 7. Comparison of Types 1 and 2 Autoimmune Hepatitis

Feature	Autoimmune hepatitis	
	Type 1	Type 2
Characteristic autoantibodies	ANA, SMA	Anti-LKM1
Associated autoantibodies	pANCA	Anti-LC1
	Anti-SLA/LP	Anti-ASGPR
	Anti-actin	
	Anti-ASGPR	
Age at onset	All ages	Mainly pediatric (2-14 years)
Common concurrent immune diseases	Autoimmune thyroiditis	Vitiligo
	Synovitis	Type 1 diabetes
	Ulcerative colitis	Autoimmune thyroiditis
Implicated genetic factors	*DRB1*0301* (N. Europe)	*DQB1*02*
	*DRB1*0401* (N. Europe)	*DRB1*03*
	*DRB1*1501* (protective)	
	*DRB1*1301* (S. America)	*DRB1*07*
Autoantigen	Uncertain	CYP2D6
Treatment	Corticosteroids	Corticosteroids

ANA, antinuclear antibodies; anti-ASGPR, antibodies to asialoglycoprotein receptor; anti-LC1, antibodies to liver cytosol type 1; anti-LKM1, antibodies to liver/kidney microsome type 1; CYP2D6, cytochrome monooxygenase 2D6; pANCA, perinuclear antineutrophil cytoplasmic antibodies; SMA, smooth muscle antibodies.

Modified from Czaja AJ. Autoimmune liver disease. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. Vol 2. 4th ed. Philadelphia: Saunders; 2003. p. 1163-1202. Used with permission.

have concurrent immune diseases, especially autoimmune thyroiditis, synovitis, or ulcerative colitis. The onset of symptoms is acute in 40% of patients; rarely, the disease may have a fulminant presentation. Twenty-five percent of patients have cirrhosis at presentation, indicating that type 1 autoimmune hepatitis has an indolent, subclinical stage that is aggressive. The target autoantigen of type 1 autoimmune hepatitis is unknown.

Type 2 Autoimmune Hepatitis

Type 2 autoimmune hepatitis is characterized by the presence of anti-LKM1 (Table 7). Type 2 autoimmune hepatitis is predominantly a disease of children (ages 2-14 years) in Europe. Among white North American adults with autoimmune hepatitis, only 4% have anti-LKM1. The target autoantigen is the cytochrome monooxygenase 2D6 (CYP2D6), which is an important drug-metabolizing enzyme. Patients with type 2 autoimmune hepatitis have a high frequency of concurrent autoimmune diseases, especially insulin-dependent diabetes mellitus, vitiligo, and autoimmune thyroiditis, and cholangiography may show autoimmune sclerosing cholangitis. The patients also commonly have organ-specific autoantibodies, such as antibodies to parietal cells, islets of Langerhans, and the thyroid. One-third of patients with anti-LKM1 express anti-LC1. In contrast to type 1 autoimmune hepatitis, patients with type 2 disease do not have pANCA. Type 2 autoimmune hepatitis responds as well to corticosteroid therapy as does type 1 disease, and it also may have an acute, occasionally fulminant, presentation that must be recognized and treated promptly.

GENETIC PREDISPOSITIONS

Type 1 autoimmune hepatitis has a strong genetic predisposition, and 85% of white northern European

and North American patients have HLA-DRB1*03, HLA-DRB1*04 or both DRB1*03 and DRB1*04 (Table 4). Susceptibility resides within the *DRB1* gene. *DRB1*0301* is the principal susceptibility allele, and *DRB1*0401* is a secondary, but independent risk factor. HLA-DRB1*03 and HLA-DRB1*04 are associated with different clinical expressions and treatment outcomes. Patients with HLA-DRB1*03 (*DRB1*0301*) are younger and respond less well to corticosteroid therapy than patients with HLA-DRB1*04 (*DRB1*0401*). Remission occurs less frequently; treatment failure occurs more often; and death from liver failure or requirement for liver transplantation is more common in these patients. In contrast, patients with HLA-DRB1*04 (*DRB1*0401*) are older, more often women, have a greater occurrence of other immune diseases, and have a higher frequency of remission during corticosteroid treatment. HLA-DRB1*15 (*DRB1*1501*) protects against type 1 autoimmune hepatitis in white northern European patients.

Different ethnic groups have different susceptibility alleles, and HLA-DRB1*13 (*DRB1*1301*) is the principal susceptibility factor in South America, especially among children (Table 4). These variations in genetic susceptibility may reflect region-specific differences in the indigenous agents that trigger the disease. Furthermore, different manifestations of autoimmune hepatitis may have different genetic associations. Type 2 autoimmune hepatitis is associated with HLA-DQB1*02, whereas the expression of anti-LKM1 is associated with HLA-DRB1*07 and the production of anti-LC1 is associated with HLA-DRB1*03. These findings suggest that certain nonpathogenic antibodies may or may not be expressed, depending on the patient's genetic predisposition.

Genetic modifiers of the autoreactive response exist outside the major histocompatibility complex. These modifiers lack disease specificity, and they work alone, in various combinations, or in synergy (epistasis) with other principal drivers of the disease to influence the clinical phenotype and disease behavior in individual patients. Polymorphisms of the vitamin D receptor gene (*VDR*), point mutation of the tyrosine phosphatase *CD45* gene, polymorphisms of the *Fas* gene (tumor necrosis factor receptor super family), mutations of the autoimmune regulator gene (*AIRE*), and polymorphisms of the interleukin (IL)-1, IL-6, and IL-10 promoter genes are part of a burgeoning catalogue of autoimmune modifiers that will continue to expand with the application of gene microarrays.

TREATMENT REGIMENS

Prednisone alone or a lower dose of prednisone 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. Each schedule 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 normal persons from the same geographic region. Also, treatment with corticosteroids may reduce hepatic fibrosis. Improvement in hepatic fibrosis occurs in conjunction with reductions in liver inflammation, and corticosteroids may facilitate the disappearance of fibrosis by suppressing inflammatory activity. Also, small case studies have suggested that cirrhosis can disappear during treatment, but this possibility must await confirmation by assays more reliably reflective of cirrhosis than conventional needle biopsy.

The absolute and relative indications for treatment are based on degrees of severity as assessed by clinical, laboratory, and histologic findings (Table 8). Patients with inactive cirrhosis, 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 immunosuppressive therapy. The diagnosis of autoimmune hepatitis does not compel the institution of treatment, nor does the absence of symptoms preclude the need for therapy.

The preferred treatment schedule is prednisone in combination with azathioprine (Table 9). The combination schedule uses a lower dose of prednisone, and it is associated with fewer corticosteroid-related side effects. It is especially useful in patients with obesity, acne, menopause, labile hypertension, brittle diabetes, emotional lability, or osteopenia (or a combination of these). The prednisone-alone schedule is useful for patients with

Table 8. Treatment Indications for Autoimmune Hepatitis

Absolute	Relative	None
Serum AST level >10-fold upper limit of normal	Symptoms (fatigue, arthralgia, jaundice)	No symptoms and mild interface or portal hepatitis
Serum AST level >5-fold normal and γ-globulin level > twice normal	Serum AST and/or γ-globulin < absolute criteria	Inactive upper limit of cirrhosis
Bridging necrosis or multilobular necrosis in liver tissue	Interface hepatitis	Decompensated inactive cirrhosis

AST, aspartate aminotransferase.

severe, preexistent cytopenia, pregnancy or contemplation of pregnancy, or active malignancy. Both regimens are similarly effective and differ only in the frequency of side effects. Azathioprine has been teratogenic in animals, but its clinical use in transplantation and inflammatory bowel disease has not documented this complication. Nevertheless, because azathioprine is not essential for treating autoimmune hepatitis, it can be avoided during pregnancy. Alternate-day corticosteroids in titrated doses have not improved histologic features, and this regimen has been abandoned in adults.

LIVER TRANSPLANTATION

Liver transplantation 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 transplantation is 75%. No findings at presentation predict prognosis and need for transplantation, and the decision to transplant should be made after a trial of corticosteroid therapy. Failure of the laboratory indices of liver inflammation and function to improve (especially the hyperbilirubinemia) within 2 weeks after the start of corticosteroid therapy is associated with a high early mortality rate. High MELD (model of end-stage liver disease) scores (≥12 points) may identify these patients early.

Autoimmune hepatitis recurs in at least 17% of patients after liver transplantation, but recurrent disease is typically mild and managed by adjustments in the immunosuppressive regimen. Progression to cirrhosis and graft failure is possible, and the condition of patients should be monitored closely for this possibility, especially if corticosteroid therapy is discontinued after transplantation. Patients who have recurrent disease typically have HLA-DRB1*03, but recurrence is not related to a mismatch of HLA markers between donor and recipient. Transplant recipients with autoimmune hepatitis also may have a higher frequency of acute and chronic cellular rejection, and they may be more difficult to wean from corticosteroid therapy.

Autoimmune hepatitis can develop de novo in children and adults who undergo transplantation for nonautoimmune liver disease. Immunosuppression with cyclosporine or tacrolimus may affect the negative selection of autoreactive immunocytes by the thymus or inhibit their apoptosis. Treatment with prednisone and azathioprine usually is effective in suppressing disease activity. De novo autoimmune hepatitis after transplantation is rare, occurring in 2.5% to 3.4% of allografts, but it can result in graft loss if not treated with corticosteroids. The possibilities of recurrent or de novo autoimmune hepatitis after liver transplantation compel consideration of this disease in all patients with acute or chronic allograft dysfunction.

RELAPSE

Relapse connotes the exacerbation of disease activity after drug withdrawal, and it is characterized by an increase in the serum level of aspartate

Table 9. Conventional Treatment Schedules

No. of weeks administered	Combination therapy		Prednisone therapy, mg daily
	Prednisone, mg daily	Azathioprine, mg daily	
1	30	50	60
1	20	50	40
2	15	50	30
Maintenance until end point	10	50	20

aminotransferase (AST) to at least threefold normal. From 50% to 86% of patients have disease relapse after remission, most often during the first 6 months after the termination of therapy (50%). The high frequency of relapse should not discourage drug withdrawal if a complete resolution of clinical, laboratory, and histologic abnormalities has been sustained. Therapy should not be instituted with the preconception that it will be indefinite.

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 tests and tissue does not ensure a sustained remission, and 60% of patients who have achieved this result still have disease relapse. Nevertheless, the pursuit of an idealized end point during initial therapy is justified because repeated relapse and re-treatment can be associated with progression to cirrhosis, liver failure, or need for liver transplantation.

Histologic improvement lags behind clinical and laboratory resolution by 3 to 8 months, and therapy should be continued for at least 3 months beyond this point of improvement. A liver biopsy assessment performed before initial withdrawal of drug therapy is the only means of confirming histologic resolution. In Europe, treatment is maintained for at least 2 years before withdrawal of drug therapy is considered. The frequency with which corticosteroid treatment can induce resolution of the disease is unclear, and the pursuit of an idealized end point must be tempered against the patient's tolerance of the medication.

Relapse justifies re-treatment with the original drug schedule, and patients usually enter another remission. Patients who have had disease relapse should be considered for long-term, low-dose prednisone or indefinite azathioprine therapy. The low-dose prednisone strategy requires a careful decrease in the daily maintenance dose until the lowest level is achieved to prevent symptoms and maintain serum AST levels below threefold the upper limit of normal. Indefinite azathioprine therapy requires induction of clinical and laboratory remission with conventional treatment and then gradual corticosteroid withdrawal as the dose of azathioprine is increased to 2 mg per kg daily.

Relapse does not preclude permanent discontinuation of medication late in the course of the disease. Twenty-eight percent of patients who have disease relapse and are re-treated eventually develop inactive disease 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 compliance with the drug regimen (treatment failure); 13% of patients develop intolerable side effects and must stop taking the medication prematurely (drug toxicity); and 13% improve but not to a degree that satisfies remission criteria (incomplete response). High-dose prednisone (60 mg daily) or prednisone (30 mg daily) in conjunction with 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.

OTHER TREATMENTS

Cyclosporine, mycophenolate mofetil, and budesonide are empiric therapies that have been used successfully in a small number of patients with disease intolerant or recalcitrant to conventional regimens. These medications are representative of an emerging repertoire of immunosuppressive agents that have site-specific actions (immunocyte activation, differentiation, and proliferation) or unique qualities (high first-pass hepatic clearance, low toxicity) (Table 10). Most clinical experience has been with cyclosporine and mycophenolate mofetil. Budesonide is the only medication that has been tested in a clinical trial, but the results of the trial have not yet been published. None of these medications has been incorporated into standard treatment algorithms or been endorsed as salvage therapy.

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. According to three small clinical experiences, mycophenolate mofetil has been an effective substitute for azathioprine and a means of eliminating corticosteroids. These experiences have been countered by the results of another small study in which 5 of 8 patients had laboratory improvement but not resolution, and corticosteroid therapy could not be withdrawn from any of them. Budesonide has been able to induce complete or partial laboratory resolution in patients with mild disease. It is being evaluated in Europe as a frontline therapy. 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. Furthermore, budesonide has been associated with side effects in patients with cirrhosis. A standard drug with a new application is 6-mercaptopurine (1.5 mg/kg daily). Limited clinical experience has indicated its value in treating patients whose condition has deteriorated with conventional corticosteroid regimens (treatment failure).

LONG-TERM SURVEILLANCE

Follow-up must be lifelong to assess tolerance of the medication, progression to cirrhosis, late

Table 10. Promising New Immunosuppressive Drugs for Autoimmune Hepatitis

Drug	Dose	Empiric uses
Cyclosporine	5-6 mg/kg daily	First-line therapy for children and adults Corticosteroid failure Corticosteroid intolerance
Tacrolimus	4 mg twice daily	Corticosteroid failure
Mycophenolate mofetil	2 g daily	Treatment failure Corticosteroid intolerance
Ursodeoxycholic acid	13-15 mg/kg daily	Variant syndrome with serum ALP level >2-fold ULN Corticosteroid intolerance Incomplete response to standard therapy
Budesonide	3 mg twice daily	First-line therapy for mild disease Ongoing clinical trial in Europe
Mercaptopurine	1.5 mg/kg daily	Treatment failure

ALP, alkaline phosphatase; ULN, upper limit of normal.

relapse after remission, treatment failure during indefinite therapy, and malignant transformation. Prognosis remains excellent despite histologic cirrhosis, probably because liver synthetic function is preserved and complications of portal hypertension are rare. Hepatocellular cancer can develop in patients with cirrhosis for at least 5 years, but it is rare (1 per 965 patient-years of observation). Recommendations for cancer screening have not been codified. The risk of extrahepatic malignancy is 1.5 times normal for patients receiving long-term immunosuppression, and tumors have diverse cell types. Standard health maintenance screening protocols should be applied.

VARIANT SYNDROMES

Patients with features of autoimmune hepatitis and another liver disease (overlap syndrome) or findings that are similar to but atypical of classic disease (outlier syndrome) constitute the variant syndromes (Table 11). Retrospective analyses have suggested that 18% of cases of autoimmune liver disease can be reclassified as a variant form. Standardized diagnostic criteria are lacking; natural history remains 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 twofold normal, 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.

Treatment is empiric and includes prednisone, prednisone in combination with azathioprine, ursodeoxycholic acid, or prednisone and ursodeoxycholic acid (Table 11). The serum level of alkaline phosphatase at presentation identifies patients with variant syndromes who may have a response to corticosteroid therapy. Patients with serum alkaline phosphatase levels less than twice the upper limit of normal can experience improvement with corticosteroid therapy; these patients typically have overlapping features of autoimmune hepatitis and primary biliary cirrhosis (AMA positivity and histologic evidence of bile duct injury). Serum alkaline phosphatase levels more than twofold the upper limit of normal and the presence of destructive cholangitis (florid duct lesion) seen on histologic examination justify treatment with prednisone and ursodeoxycholic acid.

Therapy is based on the predominant manifestations of the disease, and regimens appropriate for hepatitic, cholestatic, or equally mixed hepatitic and cholestatic features are administered (Table 11). Histologic resolution is unusual in these patients, especially in those with autoimmune hepatitis and primary sclerosing cholangitis, and the indications for therapy and the nature of treatment are directed mainly by the severity of symptoms.

Features of autoimmune hepatitis can be present in chronic hepatitis C, and HCV viremia can be present in autoimmune hepatitis. Interferon therapy in patients with autoimmune hepatitis can exacerbate the autoimmune manifestations, and corticosteroid therapy in 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 a chronic viral hepatitis. Rare patients have classic autoimmune hepatitis, including the characteristic histologic changes, and coincidental HCV infection. The chronic hepatitis C in these patients is probably a background finding, and corticosteroid therapy can improve the predominant autoimmune disease.

SUMMARY

Autoimmune hepatitis has a global distribution and affects all age groups. Its diagnosis has been codified by an international panel, and its ability to manifest as an acute or fulminant disease is recognized. Subclassifications by serologic markers do not connote different causes or outcome, and the designations are controversial. Autoantibodies are diverse and nonpathogenic. Implicated autoantigens have been cytosolic enzymes capable of transforming self-proteins or foreign proteins

Table 11. Varient Syndromes of Autoimmune Hepatitis (AIH) and Empiric Treatments

Variant syndrome	Salient features	Empiric treatment strategies
AIH and primary biliary cirrhosis	AMA positivity Cholestatic and hepatitic tests Increased serum IgM and IgG levels	Corticosteroids if serum ALP is ≤ twice ULN Add ursodeoxycholic acid if serum ALP is > twice ULN and/or florid duct lesions in liver tissue
AIH and primary sclerosing cholangitis	Ulcerative colitis Pruritus Cholestatic and hepatitic tests ALP:AST >1.5 Abnormal cholangiogram	Corticosteroids and ursodeoxycholic acid
AIH and cholangitis (possibly AMA-negative primary biliary sclerosis)	Fatigue Pruritus Cholestatic and hepatitic tests AMA negative ANA and/or SMA positive Normal cholangiogram	Prednisone, ursodeoxycholic acid, or both, depending on hepatitic and cholestatic components

ALP, serum alkaline phosphatase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; AST, serum aspartate aminotransferase; SMA, smooth muscle antibodies; ULN, upper limit of normal.

into antigenic peptides. The disease has a strong genetic predisposition, and it is closely associated with HLA-DRB1*03 and HLA-DRB1*04 in white North Americans and northern Europeans. These risk factors affect susceptibility, clinical expression, and treatment outcome. Patients with HLA-DRB1*03 are young and therapy fails or liver transplantation is required more often than for patients with HLA-DRB1*04. Corticosteroid therapy is effective for all forms of the disease, and liver transplantation is salvage therapy for decompensated disease.

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CHAPTER 32

Nonalcoholic Fatty Liver Disease

Paul Angulo, 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 and liver failure. Hence, distinguishing between hepatic steatosis and NASH has important prognostic and management implications.

NAFLD may be categorized as primary or secondary, depending on the underlying pathogenesis (Table 1). Primary NAFLD is more common and 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, although its exact prevalence and significance in these conditions is not clear. The differentiation of primary NAFLD from secondary types is important because they have different treatments and prognosis. Primary NAFLD has reached epidemic proportions in many countries, as demonstrated by several population-based studies. In the United States, 34% of the population 30 to 65 years old and 9.6% of the population 2 to 19 years old have hepatic steatosis. If these figures are extrapolated to the 2007 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 virus (HCV) infection, which affects about 4 million people. It also is almost threefold higher than alcohol-induced liver disease (about 20 million people in the United States have some degree of 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 develop complications of end-stage liver disease, as described below.

CLINICAL MANIFESTATIONS

The clinical, laboratory, histologic, and diagnostic features of NAFLD are listed in Table 2. Patients

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CT, computed tomography; HCV, hepatitis C virus; HDL, high-density lipoprotein; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Table 1. Causes of Nonalcoholic Fatty Liver Disease

Cause	Examples
Primary	Obesity, glucose intolerance, type 2 diabetes, hypertriglyceridemia, low HDL cholesterol, hypertension
Secondary	
Nutritional	Protein-calorie malnutrition, rapid weight loss, gastrointestinal bypass surgery, total parenteral nutrition
Drugs	Glucocorticoids, estrogens, tamoxifen, amiodarone, methotrexate, diltiazem, zidovudine, valproate, aspirin, tetracycline, cocaine
Metabolic	Lipodystrophy, hypopituitarism, dysbetalipoproteinemia, Weber-Christian disease
Toxins	*Amanita phalloides* mushroom, phosphorus poisoning, petrochemicals, *Bacillus cereus* toxin
Infections	Human immunodeficiency virus, hepatitis C, small-bowel diverticulosis with bacterial overgrowth

HDL, high-density lipoprotein.

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 effect of NAFLD on health-related quality of life is being evaluated. Several studies have found a significant detrimental impact on health-related quality of life of the several comorbidities that conform the metabolic syndrome and often cluster with NAFLD.

The most common clinical scenario leading to the diagnosis of NAFLD is an asymptomatic increase in the serum levels of aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) not due to viral hepatitis, iron overload, or alcohol abuse. When these other liver diseases are ruled out, NAFLD is the likely cause in the majority of cases. Aminotransferase levels, however, are increased in only 20% of the general population with NAFLD. The AST/ALT ratio is usually less than one, but this ratio increases as fibrosis advances. Fatty infiltration of the liver as detected with ultrasonography is also likely to be due to NAFLD in the majority of cases. However, these findings by themselves are not sufficient to make a diagnosis of NAFLD. Supportive clinical, serologic, and, sometimes, histologic evidence is also required.

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. In addition, prevalence rates of these risk factors are higher when compared with patients with cirrhosis of other causes, suggesting that NASH accounts for a substantial proportion of cases of cryptogenic cirrhosis. Hepatic steatosis also has been observed to disappear over time in patients with NASH-related cirrhosis, potentially masking the diagnosis. Despite this, histologic features consistent with NASH are still found in up to one-third of explant livers at transplantation for cryptogenic cirrhosis. Rarely, NASH is a consideration in patients with subacute liver failure, having been observed among those who have had silent progression to cirrhosis before an unknown stimulus precipitates liver failure.

Clinical Features Associated With Nonalcoholic Fatty Liver Disease

The most common clinical features associated with NAFLD are the components of metabolic syndrome. *Metabolic syndrome* is defined as three or more of the following: fasting glucose of 100 mg/dL or more, central obesity with a waist circumference larger than 102 cm (40 inches) in men and more than 88 cm (35 inches) in women, blood pressure of 130/85 mm Hg or higher, fasting triglyceride level of 150 mg/dL or more, and a low level of high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men and <50 mg/dL in

Table 2. Principal Clinical, Laboratory, Histologic, and Diagnostic Characteristics of Nonalcoholic Fatty Liver Disease

Feature	Characteristics
Clinical	Usually asymptomatic, sometimes mild right upper quadrant discomfort, hepatomegaly, acanthosis nigricans, "cryptogenic" cirrhosis
	Often associated with features of metabolic syndrome: diabetes mellitus, obesity, dyslipidemia (hypertriglyceridemia, low HDL cholesterol, hypobetalipoproteinemia)
Biochemical	Increased levels of AST and ALT (usually <5-fold normal)
	Increased levels of alkaline phosphatase and γ-glutamyltransferase (usually <3-fold normal)
	AST/ALT ratio <1
	Hyperinsulinemia and insulin resistance
	Dyslipidemia, 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	Alcohol intake <140 g/week (women) or <210 g/week (men)
	Liver disease of viral, autoimmune, genetic origin

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein.

women). Of patients with NAFLD, 90% have a body mass index (BMI) of at least 25 kg/m^2, 50% are obese (BMI ≥30 kg/m^2), 28% have type 2 diabetes mellitus, 55% have dyslipidemia (hypertriglyceridemia, hypercholesterolemia, or low level of HDL-cholesterol alone or in combination), and 60% have hypertension. Almost half of the patients with NAFLD have metabolic syndrome (ie, at least three features of the syndrome) (Fig. 1). Also, about 75% of lean patients (BMI <25 kg/m^2) with NAFLD have at least one feature of metabolic syndrome. Therefore, the presence of metabolic abnormalities increases the likelihood of NAFLD, but these features are common in the general population and not specific for the diagnosis.

Most patients with NAFLD who have a BMI of 35 kg/m^2 or more also meet the criteria for central obesity, as defined above. It has been demonstrated that fat with an intra-abdominal (visceral) location is metabolically different from fat with a more peripheral or subcutaneous location. The presence and severity of NAFLD correlates more strongly with central obesity than with the BMI. Some patients with NAFLD may have a BMI less than 35 kg/m^2 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%). In the United States, a difference in prevalence between adult men and women is found only among whites (42% men vs 24% women).

Biochemical Features

Serum liver enzyme abnormalities are often restricted to an increase in the level of ALT or AST (or both), usually less than fivefold normal. Aminotransferase levels in patients with NAFLD fluctuate; at any one time, 78% of patients have normal levels, but increased levels are detected in

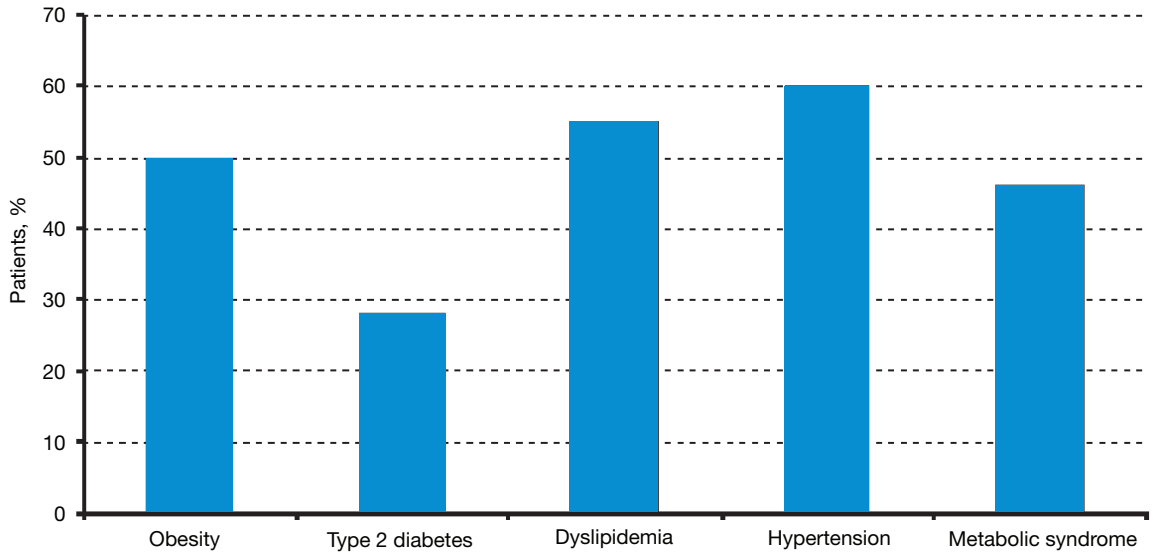

Fig. 1. The prevalence of features of metabolic syndrome among patients with nonalcoholic fatty liver disease.

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 less than threefold normal) in one-third of patients but rarely is the level of one or both of these enzymes increased without an increase in aminotransferase levels. Hyperbilirubinemia, low albumin levels, or an increase in the international normalized ratio usually indicates decompensated cirrhosis.

Serum iron tests are commonly abnormal, and 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. Whether the prevalence of heterozygous *HFE* gene mutations is increased among patients with NAFLD is debated; however, the presence of these gene mutations does not appear to be associated with hepatic iron loading or liver fibrosis. Testing for antinuclear or antismooth muscle antibodies (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 and may rarely signal coexistent autoimmune liver disease. In one series of 225 patients with NAFLD, 8% of autoantibody-positive patients also had coexistent features of autoimmune hepatitis as seen in liver biopsy specimens, but the liver biopsy features help to exclude the diagnosis of autoimmune hepatitis in most patients with NAFLD who test positive for antinuclear or antismooth muscle antibodies (or both).

Other laboratory abnormalities commonly found in patients with NAFLD are hyperglycemia, hyperinsulinemia, and increased levels of triglycerides and cholesterol and decreased levels of HDL-cholesterol.

Imaging Features

Ultrasonography, computed tomography (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 (Fig. 2). A similar pattern can be seen with diffuse fibrosis, giving rise to the term *fatty-fibrotic pattern*, although the echo shadows tend to be coarser in the presence of pure fibrosis. The sensitivity and specificity of ultrasonography for detecting hepatic steatosis vary from 60% to 94% and 88% to 95%, respectively. However, the sensitivity of ultrasonography decreases with lower degrees of fatty infiltration. In the presence of 30% or more of fatty infiltration, the sensitivity of ultrasonography is 80%

compared with a sensitivity of 55% when liver fat content is 10% to 19%. Similarly, the sensitivity and specificity of ultrasonography decrease in the presence of morbid obesity to 49% and 75%, respectively.

On noncontrast CT images, hepatic steatosis has a low attenuation and appears darker than the spleen (Fig. 3). 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 magnetic resonance phase contrast imaging techniques and magnetic resonance 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 magnetic resonance spectroscopy indicates steatosis. However, the routine application of MRI is limited by cost and lack of availability.

Histologic Features

Histologically, NAFLD is indistinguishable from the liver damage that results from alcohol abuse. Liver biopsy features include steatosis, mixed inflammatory cell infiltration, hepatocyte ballooning and necrosis, glycogen nuclei, Mallory's hyaline, and fibrosis. The presence of steatosis alone or in combination with the other features accounts for the wide spectrum of NAFLD (Fig. 4). Steatosis is present predominantly as macrovesicular fat, although some hepatocytes may show an admixture with microvesicular steatosis. When mild, fatty infiltration is concentrated typically in acinar zone 3, moderate to severe fatty infiltration shows a more diffuse distribution. The inflammatory 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's hyaline is found in about half of the 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 one of the characteristic features 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.

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's hyaline is notably sparse or absent in children with NAFLD.

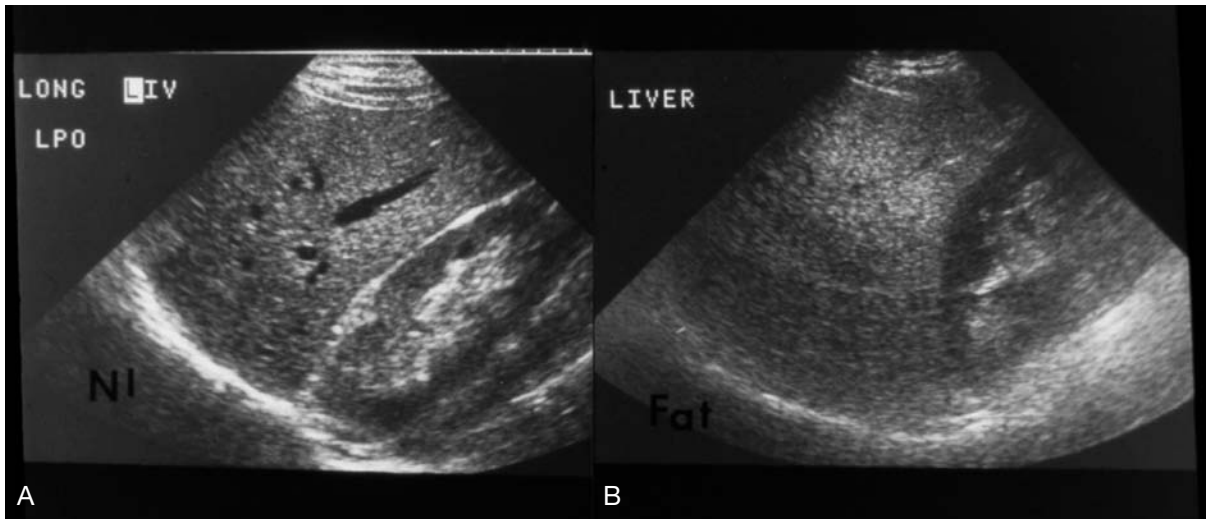

Fig. 2. Ultrasonic findings in hepatic steatosis. *A*, Normal liver has distinctive vascular features, whereas, *B*, liver with fatty infiltration has a diffuse bright echotexture and blurring of hepatic vessels.

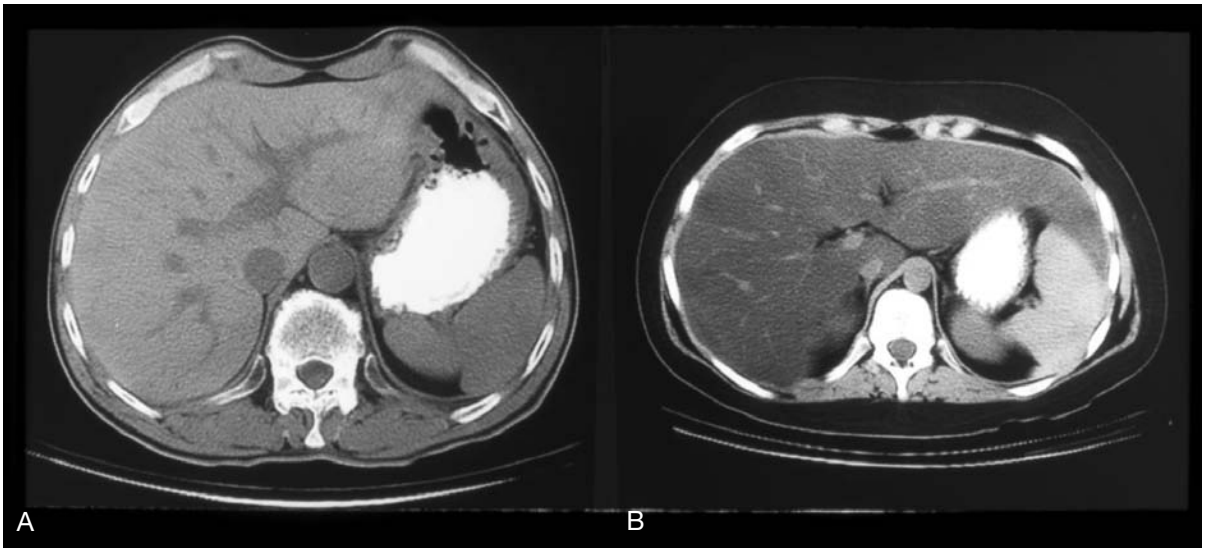

Fig. 3. Features of hepatic steatosis visualized with computed tomography. *A*, Normal liver has no attenuation of the signal compared with the spleen, whereas, *B*, liver with fatty infiltration has an attenuated signal compared with the spleen.

In some patients with cirrhotic stage NAFLD, the features of steatosis and necroinflammatory activity may no longer be present.

The histologic distinction between hepatic steatosis and NASH with high-grade inflammation and fibrosis is relatively clear; however, differentiating more subtle changes in the middle of the spectrum can be difficult. Furthermore, different histologic definitions have been used to categorize NASH. The most widely accepted definition of NASH requires the presence of zone 3 accentuated macrovesicular steatosis in conjunction with mild mixed lobular inflammation and hepatocellular ballooning. Although liver biopsy is the "gold standard" for diagnosing NASH and staging fibrosis, sampling variability may underestimate the severity of liver injury.

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 2). It is important to exclude alcohol abuse as the cause of fatty liver. It is known that a minimal amount of alcohol of 20 g/day (1-2 standard drinks) for women and 30 g/day (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 such as medications (eg, prednisolone, tamoxifen, amiodarone, and methotrexate), total parenteral nutrition, cachexia, intestinal bypass surgery, human immunodeficiency virus infection, and lipodystrophy, should be excluded because NAFLD associated with these conditions has a different course and treatment.

Patients with chronically increased serum levels of liver enzymes should have other causes excluded by clinical review and laboratory testing. The extent of laboratory evaluation should be individualized. Among patients evaluated at referral centers who have chronically increased levels of liver enzymes and a negative laboratory evaluation, the prevalence of NAFLD is between 66% and 90%. Other potential diagnoses for these patients are drug-related liver injury (7.6%), normal or nonspecific changes (5.9%-8.3%), autoimmune hepatitis (1.9%-8.3%), chronic biliary disease (3.1%-11.2%), and granulomatous liver disease (1.7%). Whether the liver should be biopsied to establish the diagnosis of NAFLD needs to be individualized. Liver biopsy may be useful for diagnosing NAFLD when a potential differential diagnosis is suggested by clinical, serologic, or biochemical

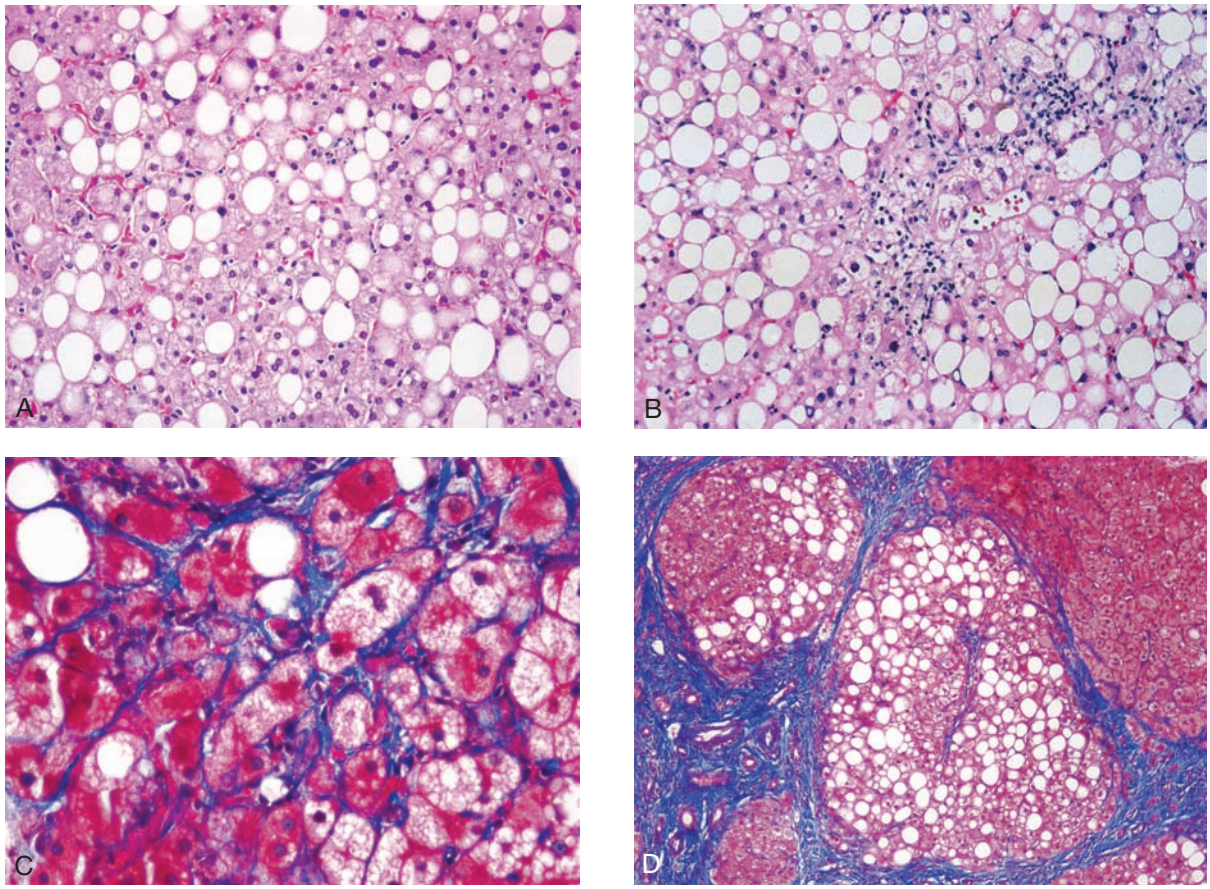

Fig. 4. Liver biopsy specimens. *A*, Bland steatosis. Steatosis is present predominantly as macrovesicular fat, although some hepatocytes may show an admixture with microvesicular steatosis. (Hematoxylin-eosin; original magnification x100.) *B*, Nonalcoholic steatohepatitis with steatosis, inflammatory infiltrate, Mallory's hyaline, and hepatocyte ballooning. (Hematoxylin-eosin; original magnification x100.) *C*, Pericellular and perisinusoidal fibrosis in zone 3. (Masson's trichrome; original magnification x400.) *D*, Cirrhotic stage of nonalcoholic fatty liver disease. (Masson's trichrome; original magnification x100.)

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 lipids 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. Imaging studies such as ultrasonography, CT, and MRI are not able to distinguish between steatosis and NASH, nor are they able to stage the degree of hepatic fibrosis. Recently, measuring liver stiffness with ultrasound- or magnetic resonance-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.

The potential benefits of liver biopsy must be weighed against the small risk of complications, including pain, bleeding, and death. The decision to pursue biopsy needs to be discussed and individualized with each patient. 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. These features have been combined in a numerical score aimed at predicting the presence or absence of advanced fibrosis in NAFLD (Table 3).

More recently, advanced fibrosis in patients with NAFLD has been associated with levels of novel 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 a numerical score named the *Enhanced Liver Fibrosis* panel to predict the presence and severity of liver fibrosis in NAFLD. Similarly, the fibrotest, which has been studied extensively in viral hepatitis to predict the severity of fibrosis, has been evaluated in NAFLD. In addition, caspase-3-generated cytokeratin-18 fragments, a marker of apoptosis measured in plasma, has been evaluated in distinguishing between simple steatosis and NASH. With plasma from 44 patients with NAFLD, Wieckowska et al reported a specificity of 99.9%, a sensitivity of 85.7%, and positive and negative predictive values of 99.9% and 85.7%, respectively, for a cytokeratin-18 value of 395 U/L for the diagnosis of NASH. Although all these scores based on laboratory markers aid in making the decision about who should have biopsy, additional validation is required before the markers can be used routinely in clinical practice.

Table 3. Clinical and Serum Markers of Fibrogenesis Proposed as Predictors of Advanced (Stage 3-4) Fibrosis in Patients With Nonalcoholic Fatty Liver Disease

Author	No. of patients	Clinical score/serum marker	AUC	Sensitivity, %	Specificity, %
Angulo et al	733	–1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IGF/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×10^9/L) – 0.66 × albumin (g/dL)	0.88		
		Score < –1.455		82	77
		Score > 0.676		51	98
Suzuki et al	79	Hyaluronic acid >46.1 ng/mL	0.89	85.0	79.7
Sakugawa et al	112	Hyaluronic acid ≥50 ng/mL	0.80	68.8	82.8
		Type IV collagen 7S ≥5 ng/mL	0.82	81.3	71.4
Palekar et al	80	Hyaluronic acid >45.3 ng/mL	0.88	85.7	80.3
Dos Santos et al*	30	Hyaluronic acid >24.6 ng/mL	0.73	82.0	68.0
		Type IV collagen >145 ng/mL	0.80	64.0	89.0
		Laminin >282 ng/mL	0.87	82.0	89.0
Ratziu et al	267	Fibrotest >0.30	0.88	92.0	71.0
		Fibrotest >0.70	0.88	25.0	97.0
Guha et al	192	–7.412 + [ln(HA) × 0.681] + [ln(P3NP) × 0.775] + [ln(TIMP1) × 0.494]	0.93	80.0	90.0
		ELF = 0.3576			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the receiver operator characteristic curve; BMI, body mass index; ELF, enchanced liver fibrosis; HA, hyaluronic acid; IGF, insulin-like growth factor; ln, logarithm negative; P3NP, propeptide of type III collagen; TIMP1, tissue inhibitor of matrix metalloproteinase-1.

**Predicting presence of fibrosis vs absence of fibrosis.*

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 239 patients for an average of 12 years showed progression to cirrhosis in 3 patients (1.3%) and liver-related death in only 2 (0.8%). In contrast, NASH may progress to cirrhosis in up to 15% of patients within 15 years after diagnosis. Therefore, the diagnosis of NASH may prompt a more aggressive therapeutic approach toward metabolic risk factors and participation of patients in clinical trials of 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. Histologic staging is also valuable for tracking disease progression or monitoring response to therapy. It is important to recall, however, that changes in aminotransferase levels do not correlate reliably with histologic changes over time.

TREATMENT

Treatment of Associated Conditions

A large body of clinical and epidemiologic data gathered during the last three decades indicates that obesity, type 2 diabetes mellitus, and hyperlipidemia are major associated conditions or predisposing factors leading to the development of NAFLD. Hence, it is reasonable to believe that the prevention or appropriate management of these conditions would lead to improvement or arrest of the liver disease (Table 4). 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. Total starvation or very low calorie diets may cause worsening of the histologic features and, thus, should be avoided. The National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases expert panel clinical guidelines for weight loss recommend that the initial target for weight loss should be 10% of baseline weight within 6 months. This can be achieved by losing about 0.45 to 0.90 kg (1-2 lb) per week. With success, further weight loss can be attempted if indicated through further assessment. The panel recommended losing weight through the use of multiple interventions and strategies, including lifestyle modification (ie, diet modifications and increased physical activity), behavioral therapy, pharmacotherapy (ie, orlistat, phentermine, or sibutramine) and surgery, as well as a combination of these treatment modalities. The recommendation for a particular treatment modality or combination should be individualized, taking into consideration the BMI and the presence of concomitant risk factors and other diseases.

Table 4. Therapeutic Options for Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Lifestyle changes	Weight reduction
	Reduce total fat intake to <30% of energy source
	Replace saturated with unsaturated fats
	Increase fiber intake to >15 g/day
	Increase physical activity
Insulin-sensitizing agents	Metformin
	Pioglitazone
	Rosiglitazone
Antioxidants and cytoprotective agents	Vitamins E and C
	Betaine
	Taurine
	N-Acetylcysteine
	Sibilin
	Ursodeoxycholic acid
	Fibrates and statins
	Orlistat, phentermine, sibutramine
Other treatments and future areas of research	Anti TNF-α antibodies
	Pentoxifylline
	Antifibrotic medications
	Angiotensin II receptor antagonists
	CB_1 receptor antagonists
	Caspase inhibitors

CB, cannabinoid; TNF, tumor necrosis factor.

The panel did not make specific recommendations for the subgroup of patients with NAFLD; however, with the lack of clinical trials in this area, the overall panel recommendations may be a useful and safe first step for obese patients with NAFLD. Similarly, no specific recommendations were made for monitoring with liver tests during weight loss; but measuring liver enzymes monthly during weight loss seems appropriate.

Different dietary caloric restrictions have been used. However, additional studies are needed to determine the most appropriate content of the formula to be recommended for obese or diabetic patients with NAFLD. In the absence of well-controlled clinical trials of patients with NAFLD, it may be tempting to recommend a heart-healthy diet, as recommended by the American Heart Association for those without diabetes and a diabetic diet as recommended by the American Diabetes Association for those with diabetes. Dietary supplementation with ω-3 polyunsaturated and monounsaturated fatty acids may improve insulin sensitivity and prevent liver damage. Saturated fatty acids worsen insulin resistance, whereas dietary fiber can improve it. Nevertheless, the effect of such dietary modifications in patients with fatty liver has not been established. A diet to produce weight loss should always be prescribed on an individual basis and in consideration of the patient's overall health. Patients who have obesity-related disease such as diabetes mellitus, hyperlipidemia, or cardiovascular disease require close medical supervision during weight loss to adjust the medication dosage as needed.

Improving insulin sensitivity with lifestyle changes or medications usually improves glucose and lipid levels in patients with diabetes and hyperlipidemia. Improving insulin sensitivity in these patients is expected to improve liver disease, but in many diabetic or hyperlipidemic patients with NAFLD, the appropriate control of glucose and lipid levels is not always accompanied by improvement in the liver condition.

Pharmacologic Treatment

Because achieving and maintaining appropriate weight control is difficult for most obese patients to accomplish, the use of medications that can reduce directly the severity of liver damage independently of weight loss is a reasonable alternative. Pharmacologic therapy also may benefit patients who do not have risk factors or associated conditions, that is, nonobese, nondiabetic patients and those with a normal lipid profile. However, pharmacologic therapy directed specifically at the liver disease has been evaluated only recently in patients with NAFLD. Most of these studies have been uncontrolled, open-label studies that lasted 1 year or less, and only a few of them evaluated the effect of treatment on the histologic features of the liver. The results of pilot studies that evaluated insulin sensitizer medications, antioxidants, lipid-lowering medications, and some hepatoprotective medications suggest that these medications may be of potential benefit, but well-designed controlled trials are needed before any of the medications can be recommended for patients with NAFLD.

General Recommendations

A useful first step in the management of patients with NAFLD is to have them make an attempt at gradual weight loss and make a concerted effort to maintain appropriate control of serum glucose and lipid levels. Perhaps this, along with appropriate exclusion of other liver disease, may be the only treatment recommendation for patients with pure steatosis and no evidence of necroinflammation or fibrosis, because these are the patients who seem to have the best prognosis within the spectrum of NAFLD. Patients with steatohepatitis, particularly those with increased fibrosis seen in liver biopsy specimens, may have a worse prognosis and should be monitored closely. They should make a greater effort to achieve adequate metabolic control and should be offered enrollment in well-controlled clinical trials that evaluate the potential benefit of promising medications. Pharmacologic therapy holds promise, but data from well-controlled clinical trials are needed to determine not only the efficacy but also the long-term safety of the several experimental medications; currently, none of these medications can be recommended for the treatment of NAFLD outside of clinical trials.

For patients with cirrhotic stage NAFLD and decompensated disease, liver transplantation is a potential life-extending therapeutic alternative, although some patients with cirrhotic stage

NAFLD have comorbid conditions that often reduce the usefulness of liver transplantation.

PREVENTION

No studies have been aimed at preventing the development of NAFLD. However, preventing the development of insulin resistance and its clinical manifestations (ie, metabolic syndrome) is expected to prevent the development of NAFLD. Weight gain and obesity resulting from an increased sedentary lifestyle and diets with a high content of fat and carbohydrates seem to be key factors in the development of insulin resistance and NAFLD. Thus, achieving and maintaining appropriate weight control would be expected to prevent the development of NAFLD, as would the treatment of glucose and lipid abnormalities. This is supported further by data from the diabetes prevention program in the United States which demonstrated that both lifestyle intervention and the insulin-sensitizing drug metformin significantly decreased the development of metabolic syndrome, which intuitively would prevent the development of NAFLD.

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CHAPTER 33

Liver Disease and Pregnancy

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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 1), including spider nevi and palmar erythema in 50% of pregnant women, increased serum level of alkaline phosphatase from placental production, and decreased serum levels of bilirubin and hemoglobin with expanded blood volume. Increased levels of bilirubin and transaminases, hepatomegaly, splenomegaly, liver tenderness, or bruits do not occur in normal pregnancy, and the clinical finding of jaundice is always abnormal. Abnormalities in liver enzyme levels occur in 3% to 5% of pregnancies and jaundice in 0.1%, with a clinical significance that is highly variable from a self-limiting to a rapidly fatal condition.

For diagnostic purposes, it is useful to divide liver diseases in pregnant women into three main categories (Table 2):

Table 1. Physiologic Changes in Liver Tests During Pregnancy

Test	Change
Bilirubin	Unchanged
AST, ALT	Unchanged
Prothrombin time	Unchanged
Alkaline phosphatase	Increases 2- to 4-fold
Fibrinogen	Increases 50%
Globulin	Increases in α- and β-globulins
α-Fetoprotein	Moderate increase, especially with twins
Leukocytes	Increase
Ceruloplasmin	Increases
Cholesterol	Increases 2-fold
Triglycerides	Increase
Globulin	Decreases in γ-globulin

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Abbreviations: AFLP, acute fatty liver of pregnancy; ERCP, endoscopic retrograde cholangiopancreatography; HBeAg, hepatitis B e antigen; HELLP, hemolysis, elevated liver tests, low platelets; ICP, intrahepatic cholestasis of pregnancy; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; UDCA, ursodeoxycholic acid.

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 (*h*emolysis, *e*levated *l*iver tests, *l*ow *p*latelets) syndrome, and acute fatty liver of pregnancy (AFLP)

These 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 and incidental and chronic liver diseases are uncommon.

DIAGNOSTIC STRATEGY IN PREGNANT PATIENTS

Optimal management of pregnant patients who have abnormal liver tests or jaundice requires accurate and often rapid diagnosis. The clinical presentation and trimester of pregnancy are diagnostically important (Table 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 transplantation) 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 or risk factors for sepsis?
7. Does the presentation fit one of the liver diseases unique to pregnancy?

Table 2. Causes and Timing of Liver Disease During Pregnancy

Disease category	Specific disease	Trimester of pregnancy
Chronic liver disease/portal hypertension	Chronic hepatitis B	1-3
	Hepatitis C	1-3
	Autoimmune disease	1-3
	Wilson's disease	1-3
	Cirrhosis of 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	2-3
	Hyperemesis gravidarum	1
	Preeclampsia	3, late 2
	HELLP syndrome	3, late 2
	Acute fatty liver of pregnancy	3

HELLP, hemolysis, elevated liver enzymes, low platelets.

Clinical features and laboratory testing allow a diagnosis in most patients, but for some patients, imaging of the liver, endoscopic retrograde cholangiopancreatography (ERCP), or liver biopsy is necessary. Ultrasonography of the liver and abdomen is safe during all three 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 for 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 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; herpes simplex 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 the pregnant and nonpregnant populations and during each of the three trimesters 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 extremely rare in the United States but is endemic to 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 fulminant 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 hepatitis E and herpes simplex, the clinical and serologic course of acute hepatitis in pregnant women is the same as in nonpregnant patients, and the hepatitis does not appear to affect the pregnant state adversely. Even though herpes simplex hepatitis is rare, it must be diagnosed because specific therapy is life-saving. 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 endemic area. 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 in which prompt therapy with acyclovir or vidarabine is life-saving and without which 50% of mothers will die. 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 section, and breastfeeding should not be discouraged.

Perinatal transmission of hepatitis B is highest in mothers with acute hepatitis, especially with hepatitis B e antigen (HBeAg)-positivity 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 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 3). 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 should be given passive immunoprophylaxis with immunoglobulin within 48 hours after birth. The benefits of immunoglobulin for babies of mothers seropositive for hepatitis C virus are unknown, and there is no effective therapy for preventing hepatitis C.

Gallstones and Biliary Disease

Increased lithogenicity of bile and biliary stasis during pregnancy predispose 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 follow 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, least common, acute cholecystitis. The clinical features of biliary disease and pancreatitis are the same as in nonpregnant patients, can occur at any time of gestation, and 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 pregnant state. For acute biliary colic or acute cholecystitis, conservative therapy with bed rest, intravenous fluids, and antibiotics is instituted initially and is successful in more than 80% of cases, 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.

Table 3. Prophylaxis Regimen for Babies of HBsAg-Positive Mothers

Preparation	Dose	Intramuscular administration
HBIG	0.5 mL	At birth
HBV vaccine*	0.5 mL (10 μg)	At birth (2 days) At 1 month At 6 months

HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.
**Recombinant vaccine.*

PREGNANT PATIENTS WITH CHRONIC LIVER DISEASE

Many women with chronic viral or autoimmune hepatitis or Wilson's disease are of childbearing age. Chronic hepatitis B is present in 0.5% to 1.5% of pregnancies and chronic hepatitis C 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 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. Gilbert's 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's disease must be treated adequately before pregnancy and continue receiving therapy throughout the pregnancy. Discontinuation of therapy poses the risk of fulminant Wilson's 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 transplantation 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 section 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 transplantation, 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 transplantation 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 2). Although still poorly understood, some interesting advances have been made recently in understanding these pregnancy-associated diseases. These diseases belong to one of two main categories depending on whether or not they are associated with preeclampsia. Second only to viral hepatitis as a cause of jaundice in pregnant patients is ICP, a disease of severe pruritus, mild jaundice, and biochemical cholestasis limited to the second half of pregnancy. In the United States, ICP occurs in 0.1% of pregnancies, with jaundice in about 20% of cases. Hyperemesis gravidarum, with an incidence of 0.3%, is intractable nausea and vomiting that occur in the first trimester; high transaminase levels occur in 50% of patients and occasionally jaundice develops. ICP and hyperemesis are not associated with preeclampsia.

The preeclampsia-associated liver diseases are preeclampsia itself, HELLP syndrome, and AFLP. Preeclampsia occurs in 5% to 10% of pregnancies, but the liver is involved only in a small proportion

of patients. Preeclampsia is the most common cause of liver tenderness and abnormal liver tests in pregnant patients.

Hyperemesis Gravidarum

Hyperemesis gravidarum is intractable 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 occur in 50% of patients, up to 20-fold above the normal range. 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, viral hepatitis serologic testing 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 MDR3 mutations has been confirmed by several investigators, and MDR3 mutations may account for 15% of cases of ICP.

The pathogenesis clearly is related in some way to female sex hormones: 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 liver metabolic response 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 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 occured 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 near-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 recent 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, 600 to 1,200 mg/day, is successful in producing relief from pruritus, with parallel improvement in liver tests, and it has no adverse maternal or fetal effects. In one study, fetal outcome was improved, with fewer premature births. High-dose UDCA, 1.5 to 2.0 g/day, has been shown recently 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 almost normal bile acid levels, as compared with 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 the latter 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 occasionally with oral contraceptives. Patients with ICP are subsequently at higher risk than the general population for the development of 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-associated liver diseases include preeclampsia itself, HELLP syndrome, and AFLP. 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 tests 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, normal-size liver. Transaminase levels vary from mild to 10- to 20-fold increases. 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 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 **h**emolysis, **e**levated **l**iver tests, and **l**ow **p**latelet count: HELLP syndrome. 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 distinguish 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 it can be earlier or up to 48 hours after delivery. HELLP syndrome is more common in multiparous 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 three criteria: 1) hemolysis with an abnormal blood smear, increased lactate dehydrogenase level (>600 U/L), and increase in indirect bilirubin; 2) aspartate aminotransferase level more than 70 U/L; and 3) a platelet count less than 100,000/mm^3 (<100×10^9/L) and, in severe cases, less than 50,000/mm^3 (<50×10^9/L). 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 (limited views) is indicated in patients with HELLP syndrome to detect liver rupture, subcapsular hematomas, intraparenchymal hemorrhage, or infarction (Fig. 1); these abnormalities may correlate with the decrease in platelet count but not with 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 (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 section, 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 section, especially primigravida remote from term in whom the cervix is unfavorable. Half of the patients will require blood or blood products to correct hypovolemia, anemia, or coagulopathy. Management remote from term is more controversial, especially if the fetal lung is immature and the maternal 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 stability during the transfer time to a tertiary referral center. With longer conservative therapy, the condition of most women with HELLP syndrome will deteriorate in 1 to 10 days after diagnosis, with a high risk of fetal loss.

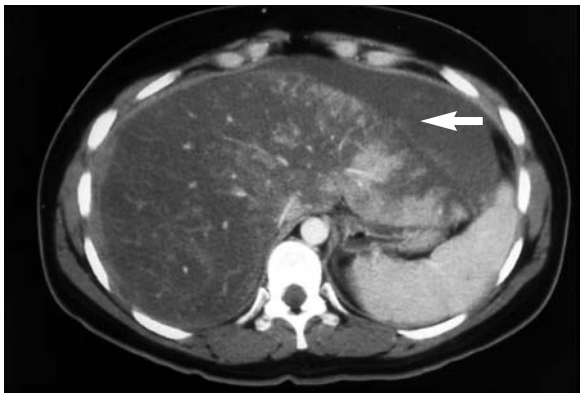

Fig. 1. Computed tomography of the abdomen of a 28-year-old woman with severe HELLP syndrome at 39 weeks' gestation. A large subcapsular hematoma (*arrow*) extends over the left lobe; the right lobe has a heterogeneous, hypodense appearance because of widespread necrosis, with "sparing" of the areas 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 increase 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, 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%), and liver failure (2%). Maternal mortality rates range from 1% to 25%. Once delivered, most babies do well.

Serious maternal complications are common in HELLP syndrome: disseminated intravascular coagulation, abruptio placentae, kidney failure, eclampsia, pulmonary edema, severe ascites, liver failure, and wound hematomas. 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%. Subsequent deliveries by these patients 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 two enzymes essential for the β-oxidation of fatty acids in liver mitochondria. Autosomally inherited genetic mutations of these two enzymes are associated most closely with AFLP, especially the G1548C mutation of *LCHAD*. 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 one 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 HELLP syndrome, 50% patients with AFLP are nulliparous, with an increased incidence in twin pregnancies. AFLP occurs almost exclusively in the third trimester, from 28 to 40 weeks, most commonly at 36 weeks. In a few patients, the presentation is jaundice in the postpartum period. The presentation can vary from asymptomatic to fulminant liver failure; 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 can vary from near-normal to 1,000 U/L, 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. Liver biopsy is rarely indicated for management but is essential for a definitive diagnosis of AFLP. Microvesicular, and infrequently

macrovesicular, fatty infiltration 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's syndrome and tetracycline and valproic acid toxicity (Fig. 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 diagnoses are AFLP, HELLP (Table 4), 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 develop complications (encephalopathy, hypoglycemia, coagulopathy, or bleeding [or a combination of these]), or whose condition continues to deteriorate despite emergency delivery, should be transferred to a liver center.

Delivery is usually by cesarean section, 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 $50{,}000/mm^3$ ($>50\times10^9/L$) 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 fulminant 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

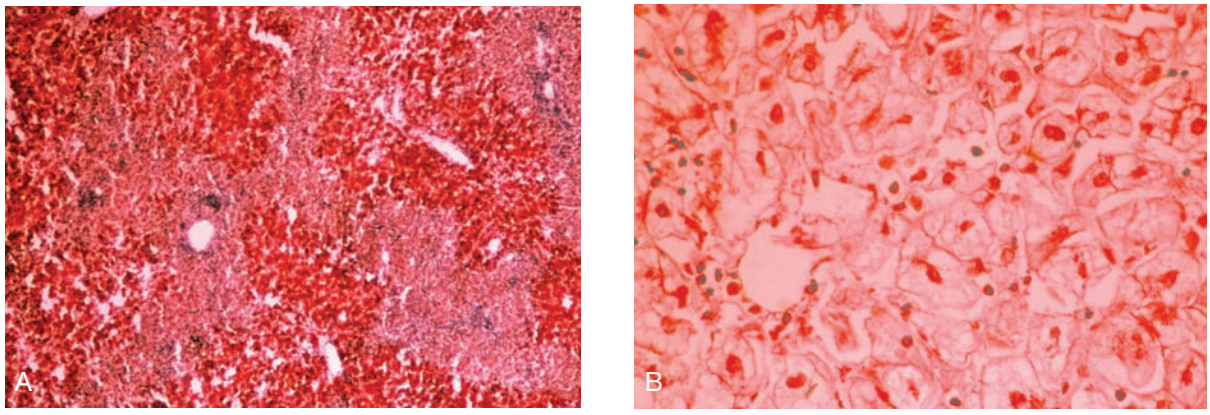

Fig. 2. Histologic appearance of the liver of a 32-year-old primigravida with acute fatty liver of pregnancy. *A*, Sudan stain (low power) shows diffuse fatty infiltration (red staining) involving predominantly zone 3, with relative sparing of periportal areas. *B*, Hematoxylin and eosin stain (high power) shows hepatocytes stuffed with microvesicular fat (free fatty acids) and centrally located nuclei.

Table 4. Diagnostic Differences Between AFLP and HELLP Syndrome

Feature	AFLP	HELLP
Parity	Nulliparous, twins	Multiparous, older
Jaundice	Common	Uncommon
Mean bilirubin, mg/dL	8	2
Encephalopathy	Present	Absent
Platelets	Low-normal	Low
Prothrombin time	Prolonged	Normal
APTT	Prolonged	Normal
Fibrinogen	Low	Normal-increased
Glucose	Low	Normal
Creatinine	High	High
Ammonia	High	Normal
Computed tomography	Fatty infiltration	Hemorrhage

AFLP, acute fatty liver of pregnancy; APTT, activated partial thromboplastin time; HELLP, hemolysis, elevated liver enzymes, low platelets.

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 transplantation 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 fulminant 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 LCHAD mutation have an increased risk of the 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 in 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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CHAPTER 34

Liver Transplantation

J. Eileen Hay, MB,ChB

Orthotopic liver transplantation (OLT) is highly effective for patients with liver failure, restoring normal health and, hopefully, a normal lifestyle. Patient survival is excellent; nationally, the survival rate is 86% at 1 year after OLT and 78% at 3 years. However, the demand for donor organs greatly exceeds supply. In the United States, about 6,500 deceased donor organs and about 300 to 500 living donor organs are available annually, but currently, more than 17,000 patients are on the liver transplant list. Patient selection and organ allocation are two major problems.

INDICATIONS FOR ORTHOTOPIC LIVER TRANSPLANTATION

Decompensated cirrhosis is the most common indication for OLT (about 70% of cases) (Table 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 (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.

Table 1. Indications for Orthotopic Liver Transplantation

Cirrhosis of any cause (CTP score ≥7)
Cirrhotic complications
Hepatocellular carcinoma
Hepatopulmonary syndrome
Acute liver failure of fulminant Wilson's disease
Primary nonfunction or early (first 7 days) hepatic artery thrombosis of hepatic allograft
Metabolic diseases
Hyperoxaluria
Familial amyloidosis

CTP, Child-Turcotte-Pugh.

Abbreviations: CTP, Child-Turcotte-Pugh; INR, international normalized ratio; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; OLT, orthotopic liver transplantation.

The two complications of cirrhosis that are accepted indications for OLT are hepatocellular carcinoma and hepatopulmonary syndrome. The following criteria (the Milan criteria) are used to select tumors suitable for OLT, that is, those likely to be cured by OLT: a single tumor 5 cm or less in any dimension or three or fewer lesions each smaller than 3 cm. For all these tumors, there can be no evidence of vascular invasion or extrahepatic spread.

About 5% of all OLTs in the United States are performed for acute medical emergencies, including acute liver failure, fulminant Wilson's 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 about only 3,000 cases annually in the United States. The most frequent cause is acetaminophen hepatotoxicity (40% of cases), followed by indeterminate causes (20%) and idiosyncratic drug reactions (14%). Primary hyperoxaluria and familial amyloidosis, diseases in which the metabolic defect is in the liver, are also recognized indications for OLT in adults. For children, several other metabolic diseases are indications for OLT. Several proposed indications for OLT are a subject of controversy, for example, cholangiocarcinoma after intensive radiotherapy and chemotherapy, portopulmonary hypertension, 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 2). The most urgent indication for OLT is acute liver failure, and these patients are given 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 two-step process: listing for OLT and allocation of a donor organ. If otherwise suitable to be a transplant recipient, a patient with cirrhosis is listed for OLT when he or she meets minimal listing criteria; this is based on a Child-Turcotte-Pugh (CTP) score of 7 or more. However, organ allocation is prioritized by 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) system.

Table 2. Allocation of Deceased Donor Organs

Allocation status		Disease category
Status 1		Acute liver failure
		Fulminant Wilson's disease
		Primary nonfunction of allograft
		Hepatic artery thrombosis (1st week after transplant)
MELD score	Calculated	Cirrhosis of any cause
	Assigned	Hepatocellular carcinoma
		Hepatopulmonary syndrome
		Hyperoxaluria
		Familial amyloidosis
		Appeal to regional review board*

MELD, model for end-stage liver disease.
**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 MELD score is based on the creatinine, bilirubin, and international normalized ratio (INR) values and is calculated according to the following formula:

$$\text{MELD score} = 0.957 \times \text{Log}_e(\text{creatinine mg/dL}) + 0.378 \times \text{Log}_e(\text{bilirubin mg/dL}) + 1.120 \times \text{Log}_e(\text{INR}) + 0.643$$

The three biochemical variables are placed in a computer program and the MELD score is calculated (www.unos.org). For MELD scores higher

than 40, the expected 3-month mortality rate for patients is 80% without OLT; for scores of 20 to 29, the rate is 20% to 25%, and for scores less than 10, patients have no excess short-term mortality.

Hepatocellular carcinoma and hepatopulmonary syndrome are accepted indications for OLT for which mortality is not reflected by the MELD score. Patients with either of these conditions are assigned MELD scores to allow OLT in 3 to 12 months (called *MELD exceptions*). In the United States, hyperoxaluria and familial amyloidosis are the other two MELD exceptions for adults. Patients with these criteria are assigned a MELD score to allow for OLT to be performed within a reasonable time (eg, for patients with hepatocellular carcinoma, the MELD score is initially 22, then increases to 25, 27, and 29 at 3-month intervals until OLT).

The only ways for patients to be guaranteed consideration for allocation of a deceased donor organ is to have status 1, a calculated MELD score, or one of the four MELD exceptions for adults (Table 2). For controversial indications for OLT or for patients who are more symptomatic than suggested by their MELD score, transplant programs may appeal to the 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 (Table 3). 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.

IMMUNOSUPPRESSION

Five main groups of immunosuppressive medications are used in OLT (Table 4). Each immunosuppressive drug has its own site of action and side effects. The risk of rejection is highest in the first weeks after OLT, at which time 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 side effects from individual drugs.

Table 3. Contraindications to Orthotopic Liver Transplantation

Absolute	Relative
Extrahepatic malignancy unless tumor-free for ≥2 years and low probability of recurrence	General debility
Untreated alcoholism or alcoholic hepatitis	Social isolation
High-dose or multiple pressors	Advanced age
Severe multiorgan failure	Extensive previous abdominal surgery
Severe psychologic disease likely to affect compliance	Extensive portal or mesenteric thrombosis
Severe pulmonary hypertension	
Advanced cardiopulmonary disease	

Table 4. Immunosuppressive Drugs and Their Side Effects

Drug class	Drug	Side effects
Corticosteroids*	Methylprednisone Prednisone	Hypertension, diabetes mellitus, neurotoxicity, hyperlipidemia, bone loss, myopathy
Purine antagonists	Azathioprine	Cytopenias
	Mycophenolate mofetil	Gastrointestinal side effects (mycophenolate mofetil only)
Calcineurin inhibitors*†	Tacrolimus Cyclosporine	Nephrotoxicity, hypertension, diabetes mellitus, neurotoxicity
TOR inhibitors	Sirolimus/rapamycin	Cytopenias, hyperlipidemia, poor wound healing, hepatic artery thrombosis
Antibody therapy (intravenous)*	OKT3 (muromonab-CD3) Antithymocyte globulin (Thymoglobulin)	Profound immunosuppression, opportunistic infections

TOR, target of rapamycin.
**Used for treatment and prevention of rejection (others used only for prevention).*
†Beware of drug interactions with drugs affecting cytochrome P-450 enzyme system; inhibitors of the cytochrome P-450 system (eg, fluconazole) increase the levels of calcineurin inhibitors; drugs stimulating the cytochrome P-450 system (eg, phenytoin) decrease calcineurin inhibitor levels and thus increase the risk of rejection.

COMPLICATIONS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

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 needs to be reactivated as status 1 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 an abscess or ischemic cholangiopathy. When hepatic artery thrombosis occurs in the first 7 days after OLT, the patient will be listed for retransplantation 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 muromonab-CD3 (OKT3) or antithymocyte globulin. Acute cellular rejection early after OLT generally has no effect on long-term graft outcome, and very few grafts are lost to chronic rejection.

Biliary Strictures

The biliary anastomosis, either duct-to-duct or biliary-enteric, 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 primary sclerosing cholangitis. Some of these strictures can be managed with endoscopic or percutaneous biliary stenting, although ischemic-type biliary stricturing leads to death or need for retransplantation in about 50% of cases.

Infections

A systemic fungal, viral, or bacterial infection develops in one in five 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 valganciclovir. *Candida* infection is the most common fungal infection, although opportunistic infections can also be seen with *Aspergillus*, *Nocardia*, *Cryptococcus*, and *Pneumocystis*. Some 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. Recurrent hepatitis C may be treated with pegylated interferon and ribavirin. Side effects are common, especially anemia, and dose reductions are frequently necessary. Treatment with pegylated interferon and ribavirin produces a sustained virologic response in about 30% of patients with recurrent hepatitis C after liver transplantation. Currently, 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 pre-OLT risk factors for coronary artery disease, treatment with immunosuppressive drugs may produce an increase in hypertension, diabetes, kidney failure, dyslipidemia, and obesity in a high percentage of patients (Table 5). This leads to a profile of high risk for cardiovascular diseases for many OLT recipients, with cyclosporine having more metabolic effects than tacrolimus. OLT recipients must receive adequate screening and treatment for these risk factors.

Table 5. Cardiovascular Risk Factors in Liver Recipients

Complication	Recipients affected, %
Hypertension*	50
Diabetes mellitus	30 (15 new-onset)
Kidney failure*	14-30
Dyslipidemia*	30-45
Obesity	20-30

**Worse with cyclosporine than with tacrolimus.*

Liver transplant recipients have multiple potential risk factors for cancer: immunosuppression, viruses (hepatitis C virus, hepatitis B virus, human papillomavirus, human herpes virus 6, Epstein-Barr virus), alcohol use, and smoking. Furthermore, many recipients are now older than 50 years or even older than 60 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. The reported overall incidence of cancer varies depending on the series, 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.

EXPANSION OF THE DONOR POOL

Adult-to-adult living donor liver transplantation (LDLT) uses the right lobe of the donor for implantation into the recipient. For pediatric recipients, the left lobe may be used, depending on size. The major advantages of LDLT over deceased donors 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 0.4% (1/250). 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, and disadvantage to primary recipient), marginal donors (eg, fatty liver with increased risk of primary nonfunction), donation after cardiac death (increased risk of biliary complications), and high-risk donors (high-risk lifestyle or medical history).

RECOMMENDED READING

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Liver

Questions and Answers

QUESTIONS

Abbreviations used:
ALT, alanine aminotransferase
AST, aspartate aminotransferase
CT, computed tomography
ERCP, endoscopic retrograde cholangiopancreatography
HAV, hepatitis A virus
HBc, hepatitis B core
HBcAb, hepatitis B core antibody
HBeAg, hepatitis B e antigen
HBs, hepatitis B surface
HBsAg, hepatitis B surface antigen
HBV, hepatitis B virus
HCV, hepatitis C virus
HDV, hepatitis D virus
HIV, human immunodeficiency virus
INR, international normalized ratio
MCV, mean corpuscular volume
MRCP, magnetic resonance cholangiopancreatography

Multiple Choice (choose the best answer)

1. A 45-year-old woman with left lower quadrant abdominal cramps is found to have a liver mass. Liver ultrasonography shows a 4-cm mass with uniformly increased echogenicity. The results of liver tests are normal. Contrast CT shows a 4-cm mass with peripheral nodular enhancement in the arterial phase and gradual fill-in of contrast in the later phases. The rest of the liver appears normal. The most appropriate management of this mass is:

a. Repeat CT in 4 months
b. Radiofrequency ablation
c. Biopsy to confirm the diagnosis
d. Surgical resection
e. No further intervention is needed

2. A 28-year-old woman with abdominal pain has a 4-cm solid liver mass and two 2-cm simple liver cysts. She has been taking oral contraceptives for 5 years but has no history of liver disease. On contrast CT, the mass enhances in the arterial phase and is isoattenuating in the venous phase. The imaging data are thought to be consistent with either focal nodular hyperplasia or adenoma. Biopsy confirms focal nodular hyperplasia. The pain has since resolved. The most appropriate management of focal nodular hyperplasia in this patient is:

a. No further intervention is needed
b. Radiofrequency ablation
c. Chemoembolization
d. Surgical resection
e. Discontinuation of oral contraceptives

3. A 35-year-old woman with dyspepsia has a 4-cm liver mass. She has no history of liver disease.

She has taken oral contraceptives for 8 years. On CT with contrast, the mass enhances rapidly in the arterial phase and is isoattenuating in the venous phase. It has areas of heterogeneity, consistent with regions of hemorrhage and necrosis within the mass. The most appropriate management of this mass is:

a. No further intervention is needed
b. Radiofrequency ablation
c. Chemoembolization
d. Surgical resection
e. Orthotopic liver transplantation

4. A 72-year-old woman has sudden onset of painless jaundice and increased levels of bilirubin and alkaline phosphatase. CT of the abdomen shows a large 15- × 11-cm lobulated cyst in the right lobe of the liver, with mass effect on surrounding structures. Biliary scintigraphy shows no connection of the cyst to the biliary tree. Aspiration yields 950 mL of cloudy yellow fluid; cytology shows reactive cells, and cultures are negative. The most appropriate management of this cyst is:

a. No further intervention is needed
b. ERCP with stent placement
c. Cyst aspiration and ethanol sclerosis
d. Surgical resection
e. Orthotopic liver transplantation

5. A 67-year-old man with chronic hepatitis C with cirrhosis, a platelet count of 80,000/mm^3 (80×10^9/L), and serum total bilirubin of 1.2 mg/dL was referred for evaluation. The α-fetoprotein level was 15.2 ng/mL. Recent abdominal CT findings were negative. EGD showed moderate-sized varices in the distal esophagus. Six months later, the α-fetoprotein level has increased to 250 ng/mL and ultrasonography shows a new 4.4-cm mass in the liver. Contrast CT shows arterial phase enhancement of the mass, with washout in the portal and venous phases. No other evidence of extrahepatic disease is found. The diagnosis is:

a. Hepatocellular adenoma
b. Hepatocellular carcinoma
c. Focal nodular hyperplasia
d. Diagnosis cannot be made without biopsy
e. Hemangioma

6. The most appropriate management for the patient in question 6 is:

a. Surgical resection
b. Radiofrequency ablation
c. Percutaneous ethanol injection
d. Transarterial chemoembolization
e. Orthotopic liver transplantation

7. A 46-year-old man presented with a 15-lb weight loss and diarrhea. He states that he has no abdominal pain or anorexia. Examination findings include a body mass index of 18 kg/m^2. Laboratory findings are as follows: alkaline phosphatase 264 U/L, ALT 62 U/L, hemoglobin 10.5 g/dL, and MCV 72 fL. A fecal occult blood test was negative, as was CT colonography. Liver ultrasonography showed mild steatosis and no dilated ducts. What would be the next most appropriate test?

a. Abdominal CT
b. Colonoscopy
c. MRCP
d. Tissue transglutaminase
e. Liver biopsy

8. A 63-year-old woman presented with a 4-hour history of abdominal pain, fever, and nausea. Physical examination shows fever, jaundice, and mild epigastric tenderness. Laboratory findings included the following: leukocyte count, 18,000/mm^3 (18×10^9/L) with left shift, bilirubin 3.6 mg/dL, alkaline phosphatase 150 U/L, AST 745 U/L, and ALT 650 U/L. Ultrasonography showed multiple small stones in the gallbladder, no bile duct dilatation, and a normal pancreas. Although treatment was started with antibiotics, she still had fever the following day. Laboratory tests were repeated: bilirubin 5.8 mg/dL, AST 84 U/L, and leukocyte count 25,000/mm^3 (25×10^9/L). Blood cultures were positive for *Escherichia coli*. Which of the following would you advise next?

a. Doppler study of hepatic vessels
b. Laparoscopic cholecystectomy
c. MRCP
d. Endoscopic ultrasonography
e. ERCP

9. A 23-year-old woman has a 2-week history of jaundice and a 24-hour history of somnolence. She became sexually active with her boyfriend 16 weeks ago, and he is HBsAg positive. Physical examination shows jaundice, disorientation, and asterixis. Laboratory findings include the following: ALT 1,648 U/L, bilirubin 12.5/7.4 mg/dL, and INR 2.4. HBsAg, anti-HCV, and anti-HAV were all negative. Which of the following would confirm the most likely diagnosis?

a. Serologic studies for herpes
b. Ceruloplasmin
c. IgM anti-HBc
d. Anti-HDV
e. Antinuclear antibody

10. A 42-year-old woman is receiving peginterferon and ribavirin therapy for hepatitis C. Pretreatment data included HCV genotype 2 and HCV RNA level of 550,000 IU/mL. A liver biopsy specimen showed periportal (stage II of IV) fibrosis. She is tolerating therapy well. Four-week HCV RNA was 500 IU/mL. She is now 3 months into treatment, and her HCV RNA is negative. Which of the following should you advise?

a. Continue combination therapy for 9 more months
b. Continue combination therapy for 3 more months
c. Stop therapy now

11. A 53-year-old man with ascites has a history of hepatitis B. Ten years ago, liver biopsy showed cirrhosis. Physical examination findings include jaundice, spider angiomas, and ascites. Laboratory findings include the following: ALT 86 U/L, bilirubin 1.3 mg/dL, albumin 2.9 g/dL, INR 1.3, hemoglobin 11.8 g/dL, leukocyte count 3,400/mm^3 (3.4×10^9/L), platelet count 49,000/mm^3 (49×10^9/L), and creatinine 1.2 mg/dL. HBsAg, IgG anti-HBc, and HBeAg are positive. HBV DNA is 600,000 IU/mL. Which of the following statements is most correct about this patient?

a. Lamivudine should be administered
b. Peginterferon should be administered
c. Entecavir should be administered
d. Give no further HBV therapy now; proceed with orthotopic liver transplantation
e. Paracentesis is contraindicated because of coagulopathy

12. A 45-year-old man comes to the emergency department with a 3-day history of fatigue and dull, constant, right upper quadrant pain. He drinks one bottle of wine daily. He used intravenous drugs 20 years ago and currently uses marijuana. He had taken two acetaminophen tablets for each of the last 2 days. Physical examination shows that the patient is alert and oriented. Other findings include the following: temperature 37.9°C, pulse 100, blood pressure 100/65 mm Hg, no asterixis, and tender hepatomegaly. Laboratory findings include the following: hemoglobin 12.5 g/dL, MCV 108 fL, platelet count 120,000/mm^3 (120×10^9/L), leukocyte count 14,900/mm^3 (14.9×10^9/L) with left shift, AST 96 U/L, ALT 45 U/L, bilirubin 2.8 mg/dL, INR 1.1, and HCV RNA positive. Ultrasonography shows a heterogeneous echotexture of the liver, no ascites, no gallstones, and no bile duct dilatation. Which of the following would you advise now?

a. *N*-acetylcysteine
b. MRCP
c. Corticosteroids
d. Chemical dependency counseling
e. Peginterferon and ribavirin

13. A 43-year-old man presents with persistent jaundice. Acute hepatitis A developed 3 months ago. At that time, ALT was 1,234 U/L, bilirubin was 8.6 mg/dL, and IgM anti-HAV was positive. He continues to have mild fatigue and pruritus but states that he has no abdominal

pain or fever and is not taking any medication. Physical examination findings are notable only for jaundice. Laboratory values are as follows: ALT 236 U/L, bilirubin 7.8/4.2 mg/dL, alkaline phosphatase 400 U/L, INR 1.3, albumin 3.7 g/dL, and γ-globulin 1.3 g/dL. Ultrasonographic findings were negative except for a small amount of gallbladder sludge. Which of the following would you do next?

a. ERCP
b. MRCP
c. Endoscopic ultrasonography
d. Liver biopsy
e. Serial monitoring of liver blood tests

14. An 80-year-old man with jaundice has a history of ischemic cardiomyopathy with biventricular failure. Six weeks ago, routine liver tests showed an alkaline phosphatase level of 180 U/L. Other liver enzymes at that time were normal. He was admitted 5 days ago after having a syncopal episode that was attributed to sudden-onset atrial flutter. Twelve hours after admission (4 days ago), the following laboratory values were obtained: AST 1,200 U/L, ALT 1,320 U/L, alkaline phosphatase 180 U/L, and bilirubin 1.2 mg/dL. Amiodarone therapy was started 4 days ago. He states that he does not have excessive alcohol use or other risk factors for liver disease. He says he does not have abdominal pain. Physical examination shows jaundice, tender and pulsatile liver, moderate edema, and no spider angiomas or encephalopathy. Laboratory findings include the following: AST 54 U/L, alkaline phosphatase 180 U/L, total bilirubin 4.3 mg/dL, and direct bilirubin 2.6 mg/dL. Ultrasonography shows sludge in the gallbladder but no bile duct dilatation. Which of the following would you recommend next?

a. Abdominal CT scan
b. Doppler study of hepatic artery and portal vein
c. MRCP
d. Treatment of cardiac failure
e. Stop amiodarone therapy

15. A 43-year-old asymptomatic Somali woman needs INH (isoniazid) for latent tuberculosis. Her primary physician asks for advice because she also has hepatitis B. The laboratory values are as follows, leukocyte count, 7,500/mm^3 (7.5×10^9/L), platelet count 250,000/mm^3 (250×10^9/L), AST 21 U/L, ALT 19 U/L, albumin 4.3 g/dL, INR 1.0, and bilirubin 1.0 mg/dL. HBsAg and anti-HBe are positive; HBV DNA is 1,600 IU/mL. Ultrasonographic findings are normal. Which of the following would you advise now?

a. Liver biopsy
b. Peginterferon
c. Lamivudine
d. Entecavir
e. Proceed with INH therapy

16. A 30-year-old man who has had HBV infection for 6 years presents with a 2-week history of anorexia, fatigue, and jaundice. He uses intravenous drugs and drinks alcohol in excess. He is not taking any medication. Physical examination shows jaundice and needle marks but no hepatosplenomegaly. The following laboratory results were obtained: bilirubin 14 mg/dL, ALT 1,579 U/L, AST 1,235 U/L, INR 1.5, HBsAg positive, IgG anti-HBc positive, IgM anti-HBc negative, HBeAg negative, HBV DNA 1,000 IU/mL, anti-HCV negative, HCV RNA negative, IgG anti-HAV positive, and IgM anti-HAV negative. Which of the following is most likely to establish the diagnosis?

a. Liver biopsy
b. Urine screen for acetaminophen
c. IgM anti-HDV
d. Urine screen for alcohol
e. α-Fetoprotein

17. A 50-year-old Somali man presents with a 2-week history of anorexia, fatigue, and jaundice. He came to the United States just 6 months ago. He is not aware of any previous HBV test results. He states that he does not have a previous history of liver disease, alcohol consumption, or medication use. Physical examination shows jaundice and splenomegaly.

Laboratory findings are as follows: bilirubin 14 mg/dL, ALT 864 U/L, AST 637 U/L, INR 1.5, HBsAg positive, IgM anti-HBc positive, HBeAg negative, HBV DNA 500,000 IU/mL, anti-HCV negative, IgG anti-HAV positive, and IgM anti-HAV negative. Ultrasonography shows a small nodular liver, recanalized umbilical vein, and splenomegaly. Which of the following is the most likely diagnosis?

a. Acute hepatitis B
b. Acute flare of chronic hepatitis B
c. Diffuse infiltrating hepatocellular carcinoma
d. Acute hepatitis C

18. A 48-year-old man is hospitalized for esophageal variceal bleeding. He underwent successful variceal ligation in the emergency department. He has a 2-month history of malaise, fatigue, and abdominal distention. He had unprotected sex with prostitutes 30 years ago. Physical examination shows moderate ascites and splenomegaly. Laboratory findings are as follows: hemoglobin 10.2 g/dL, leukocyte count 3,600/mm^3 (3.6×10^9/L), platelet count 61,000/mm^3 (61×10^9/L), INR 1.5, albumin 2.5 g/dL, HBsAg positive, IgG anti-HBc positive, HBeAg positive, HBV DNA 275,000 IU/mL, and anti-HCV negative. Which of the following is most appropriate?

a. Liver biopsy
b. Peginterferon
c. Entecavir
d. Lamivudine
e. Transjugular intrahepatic portosystemic shunt

19. A 27-year-old Asian woman has HBV infection and lymphoma. Two weeks ago, she had splenectomy and was found to have non-Hodgkin's lymphoma. The surgeon thought that the liver was normal. She needs chemotherapy and hematology consults to determine if there are any contraindications to chemotherapy. She has no family history of hepatocellular carcinoma. Physical examination findings are normal. The laboratory findings include normal liver enzymes, HBsAg positive, anti-HBe positive, and HBV DNA 1,000 IU/mL. Which of the following would you advise now?

a. Proceed with chemotherapy, no further treatment for HBV infection
b. Lamivudine
c. Peginterferon
d. Peginterferon and lamivudine
e. Liver biopsy

20. A 21-year-old prospective nursing student comes for evaluation because he was denied as a blood donor. He has no complaints and no significant past history. He states that he has no risk factors for viral hepatitis or other liver disease. He has not previously received HBV vaccine. Physical examination findings are normal. The complete blood count and liver enzymes are normal. Hepatitis markers: IgG anti-HBc is positive. IgM anti-HBc, HBsAg, anti-HBs, anti-HCV, and anti-HIV are negative. Which of the following would you advise now?

a. Check HBV DNA
b. Liver biopsy, with hepatitis B immunostaining of specimen
c. HBV vaccine
d. No further testing

21. A 43-year-old man was referred for management of hepatitis C. He has mild fatigue but is otherwise well. His medical history is notable for remote alcohol abuse and mild depression, for which he takes paroxetine hydrochloride (Paxil). He abused intravenous drugs 20 years ago. The body mass index is 33 kg/m^2. Otherwise, physical examination findings were normal. The following laboratory findings were obtained: ALT 84 U/L; normal bilirubin, albumin, and prothrombin time; platelet count 185,000/mm^3 (185×10^9/L), HCV genotype 1b, HCV RNA level 7,000,000 IU/mL. Ultrasonography showed a coarse liver echotexture and a normal spleen. Which of the following would you do now?

a. Start peginterferon and ribavirin therapy
b. Perform liver biopsy

c. Do nothing further now, reevaluate in 6 months
d. Arrange a psychiatry consultation

22. A 43-year-old man has hepatitis C genotype 1b. His HCV RNA level is 1,000,000 IU/mL. Liver biopsy showed stage II/IV disease (periportal fibrosis). You advise treatment with peginterferon alfa 2a 180 μg/week and ribavirin 1,200 mg/day. Twelve weeks after treatment was initiated, the HCV RNA level is 100,000 IU/mL. He is tolerating therapy well except that hemoglobin is 12 g/dL (was 16 g/dL). Which of the following would you advise now?

a. Continue therapy, repeat HCV RNA in 12 weeks
b. Increase the dose of peginterferon
c. Increase the dose of ribavirin, add erythropoietin
d. Stop therapy

23. A 43-year-old man has chronic hepatitis C. Laboratory findings included the following: ALT 79 U/L; normal bilirubin, albumin, and prothrombin time; HCV genotype 1b and HCV RNA level 2,000,000 IU/mL. Liver biopsy showed stage III/IV disease (septal fibrosis). After 6 months of full-dose pegylated interferon and ribavirin, ALT is now 35 U/L, and the HCV level is 100,000 IU/mL. Which of the following should you advise at this time?

a. Continue combination therapy for 3 more months and recheck HCV RNA
b. Stop therapy
c. Stop ribavirin therapy, continue treatment with peginterferon for 6 more months
d. Continue peginterferon and ribavirin therapy and add ursodiol

24. A 32-year-old woman is referred for hepatitis C. She used intravenous drugs 10 years ago. Physical examination findings are normal. The laboratory findings include the following: hemoglobin 14.4 g/dL, leukocyte count 4,000/mm^3 (4×10^9/L), platelet count 245,000/mm^3 (245×10^9/L), INR 1.0, ALT 93 U/L, bilirubin 1.0 mg/dL, albumin 4.3 g/dL, HCV RNA level 150,000 IU/mL, and HCV genotype 2. Ultrasonographic findings are normal. Which of the following would you advise now?

a. Observation
b. Liver biopsy
c. Peginterferon and ribavirin
d. No treatment now, reassess in 3 months

25. A 44-year-old man has had a painful lower extremity rash for 3 months. It has improved slightly with topical corticosteroids. His history is notable for ulcer disease 20 years ago that required blood transfusion. Physical examination shows a purpuric rash on both lower extremities. Laboratory findings include ALT 84 U/L and anti-HCV positive. Which of the following is most correct?

a. Rheumatoid factor will likely be positive
b. Oral corticosteroids should be given
c. Interferon therapy will not help the rash
d. Renal arteriography would likely show the characteristic changes of polyarteritis nodosa
e. Patient should have rheumatology consultation

26. An 18-year-old woman presents with acute jaundice and somnolence. She has no previous medical history and takes no medications. She has jaundice and is sleepy but arousable. Laboratory values are as follows: INR 1.6, AST 240 U/L, ALT 210 U/L, total bilirubin 8 mg/dL, direct bilirubin 3 mg/dL, hemoglobin 9.4 g/dL, ceruloplasmin 8 mg/dL (normal, <22 mg/dL), and 24-hour urine copper 563 μg (normal, <60 μg). Which of the following would you advise now?

a. Trientine
b. Penicillamine
c. Urgent liver transplantation
d. Intracranial pressure monitoring
e. Liver biopsy

27. A 74-year-old man presents with a 6-month history of fatigue and edema. He states that he does not drink alcohol in excess and does

not have a history of liver disease, diabetes mellitus, or risk factors for viral hepatitis. Physical examination shows anasarca and hepatomegaly. The following laboratory values were obtained: hemoglobin 9.3 g/dL, platelet count 140,000/mm^3 (140×10^9/L), total bilirubin 1.3 mg/dL, direct bilirubin 0.5 mg/dL, alkaline phosphatase 635 U/L, AST 64 U/L, protein 9.4 g/dL, albumin 1.8 g/dL, INR 1.0, calcium 11.4 mg/dL, and creatinine 2.3 mg/dL; urinalysis shows 3+ protein. Ultrasonography shows hepatomegaly but no mass or bile duct dilatation. Which of the following would you advise next?

a. Serum protein electrophoresis
b. Liver biopsy
c. Angiotensin-converting enzyme level
d. MRCP
e. HBsAg

28. A 43-year-old asymptomatic woman has abnormal liver tests. She drinks one bottle of wine daily and has a remote history of intravenous drug abuse. Physical examination showed jaundice, spider angiomas, and splenomegaly. Laboratory findings included the following: bilirubin 5.4 mg/dL, AST 121 U/L, ALT 58 U/L, INR 1.6, platelet count 34,000/mm^3 (34×10^9/L), and HCV RNA positive. Ultrasonography showed gallbladder stones, liver echotexture consistent with fat, a patent umbilical vein, and splenomegaly. In addition to cessation of alcohol, which of the following would you advise?

a. Peginterferon and ribavirin
b. Liver biopsy
c. Splenectomy
d. Laparoscopic cholecystectomy
e. Ultrasonography every 6 to 12 months

29. A 36-year-old asymptomatic man was referred with a chronically elevated level of bilirubin. He had colectomy 8 years ago for colon cancer complicating familial adenomatous polyposis. He abused intravenous drugs 15 years ago. He has no history of medication or alcohol excess. Physical examination findings were normal. The following laboratory results were obtained: total bilirubin 2.4 mg/dL, direct bilirubin 0.1 mg/dL, ALT normal, alkaline phosphatase normal, and hemoglobin normal. Ultrasonographic findings were normal. Which of the following is the most likely diagnosis?

a. Metastatic adenocarcinoma to the liver
b. Primary sclerosing cholangitis
c. Chronic hepatitis C
d. Gilbert's syndrome
e. Adenocarcinoma of the ampulla of Vater

30. A 36-year-old woman presents with confusion. She was found by her boyfriend, who said that the patient has been ill recently with an upper respiratory tract infection. She drinks four to six glasses of wine daily. Physical examination findings were as follows: temperature 37.5°C, heart rate 100 beats/minute, blood pressure 100/60 mm Hg. The patient was sleepy but arousable, had mild jaundice but no hepatosplenomegaly, ascites, or edema. Laboratory values were as follows: AST 5,487 U/L, ALT 5,682 U/L, bilirubin 2.5 mg/dL, alkaline phosphatase 163 U/L, NH_3 94 μmol/L, and creatinine 2.0 mg/dL. A complete blood count was normal. Which of the following would you advise at this point?

a. Pentoxifylline
b. *N*-acetylcysteine
c. Corticosteroids
d. Liver biopsy
e. Acyclovir

31. A 63-year-old asymptomatic woman was referred because of an abnormal ALT value 2 months after starting treatment with atorvastatin 20 mg/day. The pretreatment ALT value was normal. She has no risk factors for liver disease. Physical examination shows mild obesity. On laboratory testing, AST and ALT are both 65 U/L and alkaline phosphatase, bilirubin, INR, and albumin values are normal. What would be the next best step?

a. Continue atorvastatin and measure ALT again in 3 months

b. Liver biopsy
c. Liver ultrasonography
d. Stop atorvastatin therapy
e. Check antimitochondrial antibody, antinuclear antibody, HBsAg, and anti-HCV

32. A 73-year-old man presents with a 1-week history of jaundice. During this week, he also had mild anorexia and a 5-lb weight loss but said he had no abdominal pain. He has no previous history of liver disease. He drinks two beers daily. Four weeks ago, he took amoxicillin-clavulanate for 10 days for sinusitis. Physical examination documents jaundice and no fever. Laboratory findings include the following: ALT 105 U/L, alkaline phosphatase 478 U/L, and bilirubin 7.4 mg/dL. A complete blood count, INR, and albumin level are normal. Liver ultrasonography is negative. One week later, his symptoms and laboratory values have not changed, and another ultrasonographic study is negative. What would be the best next step?

a. Observe and repeat laboratory tests in 1 week
b. Liver biopsy
c. Abdominal CT scan
d. Check antimitochondrial antibody
e. MRCP

33. A 59-year-old woman presents with fatigue of 2 weeks' duration. She has no history of liver disease. Her only medical history is hypothyroidism and chronic urinary tract infections. She drinks one beer daily. Her medications include estrogen (8 years), nitrofurantoin (1 year), and levothyroxine (10 years). Physical examination findings are normal. A complete blood count is normal. Other findings include the following: ALT 533 U/L, alkaline phosphatase 135 U/L, and bilirubin 2.3 mg/dL; INR and albumin level are normal; antinuclear antibody 1:320, smooth-muscle antibody 1:80, γ-globulin 2.4 g/dL. Ultrasonography showed small gallbladder stones and no bile duct dilatation. What is the most likely diagnosis?

a. Autoimmune hepatitis
b. Nitrofurantoin-induced liver disease
c. Estrogen-induced liver disease
d. Choledocholithiasis
e. Primary biliary cirrhosis

34. A 35-year-old man presents with abdominal distention. He has a history of ulcerative colitis but had been well until the distention started suddenly 1 week ago. He states that he has no edema, dyspnea, chest pain, or fever. The liver enzyme values were normal 1 month ago. He drinks two beers daily. His medications include azathioprine and mesalamine. Physical examination showed moderate ascites. Laboratory values included the following: complete blood count normal, alkaline phosphatase 133 U/L, and ALT 85 U/L. Bilirubin, INR, and albumin values are normal. Ultrasonography showed ascites, patent hepatic and portal veins, and no bile duct dilatation. What is the most likely diagnosis?

a. Primary sclerosing cholangitis
b. Sinusoidal obstruction syndrome
c. Hepatic vein thrombosis
d. Right heart failure
e. Mesalamine-induced liver disease

35. A 43-year-old man is homozygous for C282Y. His serum iron level is 220 μg/dL, percent saturation is 88%, and ferritin is 575 μg/L. Liver test results are normal. He is healthy and asymptomatic. He consumes one alcoholic beverage daily. Physical examination findings are normal. What would you recommend?

a. No further evaluation
b. Liver biopsy
c. Phlebotomy
d. Stop alcohol and repeat iron tests in 3 months

36. A 45-year-old woman had an increased serum level of ferritin and anti-HCV detected during an evaluation for abnormal liver tests. Physical examination showed mild splenomegaly. Laboratory findings included the following: iron 120 μg/dL, percent saturation 35%, ferritin 414 μg/L, hemoglobin 13 g/dL, platelet count 109,000/mm^3 (109×10^9/L), AST 95 U/L,

ALT 134 U/L, and HCV genotype 2. Bilirubin, INR, and albumin values were normal. Ultrasonography showed a coarse liver and splenomegaly. Esophagogastroduodenoscopy showed small varices. Which of the following would you advise?

a. Liver biopsy
b. Phlebotomy
c. *HFE* gene test
d. Peginterferon and ribavirin

37. A 55-year-old man presented with increased serum iron levels. He has diabetes mellitus, arthritis, impotence, and atrial fibrillation. He consumes two to three beers each week. Physical examination detected an irregular heart rhythm. Laboratory findings included the following: iron 210 μg/dL, percent saturation 90%, and ferritin 1,714 μg/L. Liver tests and *HFE* gene tests were normal, as were ultrasonographic findings. Which of the following would you recommend?

a. No additional evaluation
b. Therapeutic phlebotomy
c. Liver biopsy
d. Magnetic resonance imaging to examine for hepatic iron deposition

38. A 32-year-old asymptomatic man who does not have any significant medical history was referred because of abnormal liver test results. Physical examination showed a body mass index of 28.4 but no stigmata of chronic liver disease. Laboratory findings included AST 64 U/L, ALT 85 U/L, and normal alkaline phosphatase and bilirubin levels. Ceruloplasmin was 17.5 mg/dL (normal, 22.9-43.1 mg/dL). Other tests for chronic liver disease were negative. What would you recommend?

a. Liver biopsy
b. Trial of weight loss and repeat liver tests
c. Slit-lamp examination to look for Kayser-Fleischer rings
d. Check serum free copper level
e. Start treatment with penicillamine

39. A 42-year-old woman has a chronic, asymptomatic mild increase in AST and ALT levels. Liver function is normal. She has a history notable for dermatomyositis, for which she takes prednisone 10 mg/day. She drinks four glasses of wine daily. Her body mass index is 23. Laboratory findings include the following: AST 94 U/L, ALT 56 U/L, alkaline phosphatase 123 U/L, and bilirubin 1.0 mg/dL. Anti-HCV, HBsAg, creatine kinase, aldolase, and iron studies are negative or normal. Ultrasonography shows a change in liver echogenicity consistent with fat. Which of the following is the most likely diagnosis?

a. Alcoholic liver disease
b. Nonalcoholic fatty liver disease
c. Celiac disease
d. Autoimmune hepatitis
e. Increased aminotransferase levels from muscle injury

40. A 47-year-old asymptomatic man presents with abnormal iron tests. He drinks two beers daily. Physical examination findings are normal. Laboratory values are as follows: iron 180 μg/dL, percent saturation 88%, ferritin 1,075 μg/L, complete blood count normal, and AST 42 U/L. The *HFE* gene test detected two copies of the C282Y mutation. Ultrasonographic findings are normal. What would be the most appropriate next step?

a. Liver biopsy
b. Therapeutic phlebotomy
c. Stop alcohol, repeat iron tests in 1 year
d. Magnetic resonance imaging of the liver

41. A 65-year-old man presents for assessment of hyperbilirubinemia of 3 weeks' duration. He has no history of inflammatory bowel disease, and colonoscopy 1 year ago was negative. Two ERCP studies showed changes consistent with primary sclerosing cholangitis, with a prominent distal bile duct stricture. On both occasions, brushings were negative for malignancy. Jaundice and mild muscle wasting were detected on physical examination. Laboratory findings included the following: hemoglobin

12.5 g/dL, leukocyte count 6.4 × 10^9/L, erythrocyte sedimentation rate 55 mm/hour, AST 30 U/L, alkaline phosphatase 506 U/L, bilirubin 8.5 mg/dL, CA19-9 <15, prostate specific antigen 0.5 ng/mL, γ-globulin 3.0 g/dL. CT showed dilated bile and pancreatic ducts and diffuse enlargement of the pancreas. Which of the following would you advise at this point?

a. MRCP
b. Repeat ERCP
c. Endoscopic ultrasonography
d. IgG4
e. Antimitochondrial antibody

42. A 36-year-old man with a history of intravenous drug use is found to be positive for HIV and HCV infection. He is asymptomatic. Laboratory findings included the following: AST and ALT both 65 U/L; complete blood count, bilirubin, albumin, and INR values normal; HCV genotype is 2, with a level of 400,000 IU/mL; HIV level is 1,000 copies/mL; and CD4 count 500/mm^3. A liver biopsy specimen showed grade 2 inflammation and stage III fibrosis. What is the most suitable therapy at this point?

a. Simultaneous introduction of antiretroviral therapy and peginterferon and ribavirin
b. Simultaneous introduction of antiretroviral therapy and peginterferon
c. Peginterferon and ribavirin
d. Antiretroviral therapy

43. A 63-year-old woman was referred for evaluation of an abnormal AST level. One year ago, the AST value was normal. Three months ago, routine testing showed AST was 84 U/L. Recently, the value was 243 U/L. She has mild fatigue but no other symptoms. She drinks one glass of wine per week. Her past medical history is notable for breast cancer and hypertension. Her medications include atenolol and tamoxifen. Findings include the following: body mass index 28, AST 243 U/L, ALT 263 U/L, alkaline phosphatase 93 U/L. Bilirubin, albumin, prothrombin time, and a complete blood count are normal. Ultrasonography shows changes in the liver consistent with fat. What would you advise now?

a. Stop tamoxifen
b. Liver biopsy
c. Weight loss and repeat tests in 3 months
d. CT scan of the liver
e. Stop drinking alcohol

ANSWERS

1. Answer e

The best answer is "e" because the CT description is classic for a cavernous hemangioma, which is a benign lesion that requires no therapy unless it is symptomatic. The symptom of left lower quadrant abdominal cramps is not the usual symptom for a subcapsular hemangioma, which typically causes a pleuritic type pain that is due to irritation of the diaphragm and is worse with deep inspiration. Repeat CT would not be unreasonable to confirm the diagnosis if it is in doubt or to ensure that the lesion is stable, but it is not the best answer because the radiologic appearance is classic for the condition. Radiofrequency ablation is not indicated for treatment of cavernous hemangiomas. Biopsy is needed only if the diagnosis is in doubt. Surgical resection is indicated only for symptomatic hemangiomas.

2. Answer a

The best answer is "a" because this asymptomatic lesion is confirmed histologically to be focal nodular hyperplasia. Radiofrequency ablation is not indicated for benign liver masses except when the patient has a comorbid condition that makes him or her ineligible for surgical resection. Chemoembolization is not indicated for benign disease. Surgical resection is not needed in this now asymptomatic patient. The role of oral contraceptives in the growth of focal nodular hyperplasias is debated. It is likely that the sensitivity of focal nodular hyperplasias to oral contraceptives is limited to telangiectatic focal nodular hyperplasias, which are now considered to be a variant of hepatic adenomas.

3. Answer d

The best answer is "d" because this lesion has the typical radiologic imaging characteristics of a

hepatic adenoma, which carries a risk of future malignant transformation (particularly if it stains positive for cytoplasmic or nuclear β-catenin) or intra-abdominal hemorrhage. "No intervention" is not appropriate in this setting because of the potential risks. If surgery or another ablative method is not feasible, periodic radiologic follow-up is indicated. Radiofrequency ablation is indicated only when the patient has a comorbid condition that makes him or her ineligible for surgical resection. Chemoembolization is not indicated for benign disease. Orthotopic liver transplantation is indicated only rarely for patients with adenomatosis who have progressive replacement of the liver parenchyma, who have a high propensity for malignant transformation, or who have associated glycogen storage disease with poor metabolic control.

4. Answer c

The best answer is "c" because it represents the least invasive means of decompressing the cyst, relieving the obstruction of the central bile ducts, and preventing cyst recurrence. "No intervention" is not appropriate because the cyst is causing symptomatic biliary obstruction. ERCP with stent placement would commit the patient to long-term biliary stenting to maintain biliary patency. Surgical resection is a reasonable alternative but is considered a second-line treatment in this case because there are not any features that raise concern about malignant degeneration of the cyst. With only a single large cyst and no substantial compromise of liver function, liver transplantation is not needed.

5. Answer b

The best answer is "b" because a new lesion occurring in a cirrhotic liver with features of arterial enhancement and portal venous phase washout on cross-sectional contrast imaging meets the criteria for noninvasive diagnosis of hepatocellular carcinoma. Also, the α-fetoprotein has increased to a level that allows diagnosis of hepatocellular carcinoma with reasonable specificity. Adenomas typically have heterogeneous early arterial enhancement, with rapid return to the intensity of the surrounding liver. Like adenomas, focal nodular hyperplasias typically show early arterial enhancement, with rapid return to the intensity of the surrounding liver; also, they often have a central scar. Noninvasive diagnosis of hepatocellular carcinoma avoids the small but real risks of hemorrhage or tumor seeding along the needle tract. Hemangiomas typically show early peripheral nodular enhancement, with fill-in toward the later phases.

6. Answer e

The best answer is "e" because it represents the most definitive treatment of hepatocellular carcinoma that meets the Milan criteria (one nodule up to 5 cm large or two or three nodules up to 3 cm large) and occurs in a patient with no evidence of extrahepatic spread. Surgical resection is not appropriate because of evidence of clinically significant portal hypertension, reflected by the esophageal varices, thrombocytopenia, and increased bilirubin level. Because of the large size of the mass, the likelihood of complete ablation is not high. In this context, radiofrequency ablation does not have an effect on the underlying liver disease, which will have a propensity for the development of new tumors. Like radiofrequency ablation, percutaneous ethanol injection will not have any effect on the underlying liver disease. Transarterial chemoembolization can be used to prevent tumor progression while the patient is awaiting liver transplantation, but it is not the optimal definitive treatment for a patient who is eligible for liver transplantation.

7. Answer d

This patient presents with symptoms that are consistent with malabsorption. He has iron deficiency anemia without evidence of gastrointestinal tract blood loss. Because it would be important to exclude celiac disease, tissue transglutaminase would be the most appropriate next test. Liver tests are commonly abnormal in patients with celiac disease, and a diagnosis of celiac disease should be considered in patients with indeterminate abnormalities of liver tests. Abdominal CT is not likely to add further information to the CT colonography and liver ultrasonography. Colonoscopy should be considered in a patient with iron deficiency anemia but is not necessary because of the negative CT colonography findings and the evidence suggesting malabsorption. Similarly, MRCP

is not likely to add anything to the CT and ultrasonographic studies. Liver biopsy could be considered, but the findings would likely be nonspecific and not contribute to a specific diagnosis.

8. Answer e

This patient presents with abdominal pain, fever, and transient abnormalities of aminotransferase levels associated with a high bilirubin level. These features are suggestive of cholangitis, and this patient remains ill despite receiving antibiotic therapy. ERCP would be the most appropriate next test because it would allow not only for the diagnosis but also for removal of a common bile duct stone. Transient, marked (up to 1,000 U/L) abnormal aminotransferase levels are common in patients with acute increases in biliary pressure, as from a bile duct stone. Rapid improvement in aminotransferase levels can either indicate passage of a stone or, as is likely in this case, the stone floating back more proximally into the biliary tree. A Doppler study of the hepatic vessels would not likely add to the ultrasonographic information. Hepatic ischemia could be included in the differential diagnosis, but it generally requires systemic hypotension. It would be very unusual for someone to develop clots of both the hepatic artery and portal vein. The patient ultimately will need laparoscopic cholecystectomy, but this should be deferred until the infection has been better assessed. MRCP and endoscopic ultrasonography are helpful in diagnosing common bile duct stones but offer no therapeutic potential. Because bile duct obstruction is highly suspected in this patient, one should proceed directly with a test that offers not only diagnostic but also therapeutic benefits.

9. Answer c

This woman presents with fulminant liver failure. She has exposure to a person with hepatitis B, and the suspicion for acute hepatitis B is high. About 20% of patients with fulminant liver failure from hepatitis B are HBsAg negative. It is thought that the acute liver injury is due to a prompt and vigorous immune response to the viral infected hepatocytes. Although this may result in clearance of HBsAg, it can produce severe liver injury, seen in this case. The recent exposure to hepatitis B could be confirmed best with an IgM anti-HBc assay. Herpes hepatitis characteristically is anicteric and accompanied by very high aminotransferase levels, often more than several thousand. Acute Wilson's disease should be considered, although it would be less likely in this patient who has exposure to hepatitis B. Hepatitis D generally affects only people who are HBsAg positive. Antinuclear antibody determination can be considered because autoimmune hepatitis can occasionally present acutely. Autoimmune hepatitis is an uncommon cause of fulminant liver failure and would be less likely given the patient's exposure to hepatitis B.

10. Answer b

The patient has hepatitis C with genotype 2. At 4 weeks, her HCV RNA is positive; that is, she has not achieved a rapid virologic response but is now HCV RNA negative at 3 months. The recommendation would be to continue treatment for a total of 24 weeks. A 12- or 16-week course of therapy can be considered for patients with genotype 2, but only if the patient is HCV RNA negative at 4 weeks. Twelve months of therapy for genotype 2 patients is not significantly more effective than a 24-week course.

11. Answer c

This patient has chronic hepatitis B and has now developed decompensated liver disease. He has evidence of active viral replication, with a positive test for HBeAg and an HBV DNA level that is more than 20,000 IU/mL. This would be consistent with HBeAg-positive chronic hepatitis B with evidence of liver decompensation. Treatment is advised. The treatment administered should result in rapid improvement in HBV DNA and be accompanied by a low risk of resistance. Entecavir would be the best treatment for this patient. Lamivudine would likely produce a rapid decrease in HBV DNA, but it is accompanied by a high rate of resistance and generally is not advised for patients with decompensated cirrhosis. Peginterferon can be effective for hepatitis B but should not be given to patients with decompensated cirrhosis. The patient should certainly be considered for liver transplantation; however, therapy before transplantation is advised. Not only might therapy produce clinical improvement, but even if transplantation proves to be necessary, the decrease in HBV DNA would be accompanied by a lower

rate of posttransplant recurrence. Paracentesis is advised in patients with cirrhosis and the new onset of ascites and is not contraindicated unless coagulopathy is severe.

12 . Answer d

This patient presents with strong clinical evidence of alcoholic hepatitis. Patients with alcoholic hepatitis commonly have mild fever and leukocytosis, but clearly infection needs to be excluded. As is common in patients with alcoholism, the patient also is hepatitis C RNA positive. Chemical dependency counseling would certainly be advised because abstinence may improve the patient's clinical symptoms. Patients with acetaminophen hepatotoxicity, for which *N*-acetylcysteine might be prescribed, have a marked increase in aminotransferase levels. Although the dose necessary to produce liver injury in alcoholics is lower than it is in patients who do not consume alcohol chronically, the low dose of acetaminophen taken by this patient would not produce liver injury. MRCP could be considered if bile duct obstruction were highly suspected; however, given the clinical history and the normal ultrasonographic findings, it would not be necessary in this patient. Corticosteroids are considered as therapy for acute alcoholic hepatitis. Corticosteroids generally are prescribed for patients who have severe disease, which is defined as having encephalopathy or a discriminant function higher than 32. In patients who have a discriminant function less than 32 and hepatitis C, corticosteroids would be best avoided. Peginterferon and ribavirin therapy is less effective for patients who consume alcohol regularly and should be deferred until the patient is abstinent from alcohol. Furthermore, hepatitis C treatment should be deferred until infection has been excluded completely.

13. Answer e

This patient presents with persistent cholestasis after hepatitis A infection. This syndrome is seen in 10% of patients who acquire acute hepatitis A. No tests are necessary other than serial monitoring of liver blood tests. Further diagnostic studies such as ERCP, MRCP, and endoscopic ultrasonography can be considered if the suspicion for biliary injury is high. Biliary injury is not likely because of the absence of bile duct dilatation seen on ultrasonography and the significantly increased ALT level. Liver biopsy is not likely to add to the information that is available. Further diagnostic studies would be considered if the patient's condition does not improve with observation.

14. Answer d

This patient presents with jaundice after an episode of hypotension that resulted in acute transient increases in aminotransferase levels. This would be consistent with cholestasis after acute liver injury due to hepatitic ischemia. Because of the dual blood supply of the liver, hepatic ischemia generally occurs only in patients who have an episode of hypotension. Patients with chronic heart failure with an element of hepatic congestion are more predisposed to hepatic ischemia because they are more dependent on hepatic arterial flow. For this patient, treatment would be to try to optimize management of his cardiac failure. Abdominal CT would not be necessary because the ultrasonographic findings are negative. A Doppler study of the hepatic artery and portal vein is not necessary because hepatic ischemia requires systemic hypotension. MRCP can be considered if bile duct obstruction is a consideration. Although transient obstruction of the bile duct by a stone can produce transient abnormalities in aminotransferase levels, it usually is accompanied by abdominal pain, which is not seen in this patient. Amiodarone can result in liver toxicity, but aminotransferase levels started to increase before amiodarone therapy was instituted. Amiodarone is an important medication in treating atrial arrhythmias and would be important in managing this patient with severe cardiac disease.

15. Answer e

This patient has normal aminotransferase levels, is positive for anti-HBe, and has an HBV DNA level that is less than 20,000 IU/mL. All this would be consistent with an inactive carrier phase of hepatitis B, and treatment of hepatitis B would not be advised. Because the patient is an African woman with hepatitis B, surveillance for hepatocellular carcinoma is recommended, but she can proceed with INH therapy. Liver biopsy usually is not necessary for patients in the hepatitis B inactive carrier state. The patient should be followed with serial

monitoring of liver tests and HBV DNA, because about 5% of patients per year will have reactivation of hepatitis B.

16. Answer c

This patient with chronic hepatitis B presents with a clinical syndrome consistent with acute hepatitis. The most likely cause in a patient who abuses intravenous drugs is hepatitis D, and testing with IgM anti-HDV is advised. The other major diagnostic consideration in this case is a flare of hepatitis B. Patients with an acute flare of hepatitis B often become IgM anti-HBc positive and have high HBV DNA levels. Liver biopsy would be a reasonable consideration, but it is more invasive than serologic testing and the findings may be nonspecific. Acetaminophen hepatotoxicity usually produces significantly higher aminotransferase levels than reported in this patient. Also, he has no history of acetaminophen use. Alcoholic hepatitis is characterized by an AST:ALT ratio of 2:1 and the AST level is not higher than 400 U/L. Occasionally, disseminated hepatocellular carcinoma can produce acute hepatitis, but this is not likely in this patient who has had hepatitis B for only 6 years.

17. Answer b

This patient presents with an acute hepatitis syndrome but also with strong evidence of chronic liver disease, including a small nodular liver and a recanalized umbilical vein. This would be suggestive of acute-on-chronic disease, likely due to hepatitis B. The IgM antibody to HBc is conventionally considered a serologic marker for acute hepatitis B but can also become positive during a hepatitis B flare in someone who has long-standing hepatitis B, which is the case in this patient. Acute hepatitis B is unlikely because of the strong clinical evidence of portal hypertension. The antibody to hepatitis C does not exclude acute hepatitis C, but it is unlikely because of the evidence of hepatitis B. The patient is certainly at risk for a diffuse infiltrating hepatocellular carcinoma, but this is a relatively unusual cause of acute hepatitis and is unlikely given the lack of ultrasonographic evidence.

18. Answer c

This patient has hepatitis B with cirrhosis and a recent episode of variceal bleeding. He is positive for HBeAg and has a hepatitis B virus DNA of 275,000 IU/mL. Patients with hepatitis B and cirrhosis and any detectable HBV DNA level should be treated. Entecavir is the most appropriate agent. Lamivudine could be prescribed, but it is frequently complicated by the development of resistance, which sometimes can be accompanied by a clinical flare, which ideally should be avoided in patients with cirrhosis. Pegylated interferon is contraindicated for patients with decompensated cirrhosis. As long as the patient's bleeding is controlled with variceal ligation, transjugular intrahepatic portosystemic shunt is not needed. Patients with chronic liver disease and strong clinical evidence of cirrhosis do not require biopsy for histologic confirmation.

19. Answer b

This patient is an inactive hepatitis B carrier and needs chemotherapy. The recommendation is that patients should be treated with an antiviral agent during the course of chemotherapy and for 6 months afterward to prevent an acute flare of hepatitis B. Lamivudine would be a good choice because the length of treatment will be relatively short, which lessens the risk of the development of resistance. Pegylated interferon should be avoided if the patient is about to receive cytotoxic chemotherapy. There is no need for liver biopsy in this patient because the liver enzyme levels are normal and the HBV DNA level is low.

20. Answer c

The reasons for an isolated positivity for anti-HBc include acute hepatitis B, previous hepatitis B with disappearance of anti-HBs, ongoing hepatitis B with HBsAg below the level of detectability, and a false positive test. The fact that the antibody is IgG positive excludes acute hepatitis B. For this patient who will be a health care worker, hepatitis B immunity needs to be provided, and hepatitis B vaccine is advised. If the anti-HBc is the result of a previous infection, the patient will have an anamnestic response, with rapid development of high titers of anti-HBc. If the patient happens to have hepatitis B and receives the hepatitis B vaccine, there should be no adverse consequences, but immunity will not develop. After vaccination, the development of anti-HBs should be assessed. In a patient

who is at high risk for hepatitis B, checking HBV DNA in the serum before vaccination would be reasonable; however, most patients will be negative. Thus, this is not a cost-effective test for someone without risk factors. Liver biopsy is not needed. If this patient were not a health care worker, no further testing would be reasonable, but immunization should be ensured for this patient.

21. Answer b

This patient has hepatitis C genotype 1, with a high viral level. There is no definite evidence of cirrhosis. The general recommendation for patients with hepatitis C genotype 1, particularly if there is a relative contraindication to treatment, such as depression, is to proceed with liver biopsy. Patients with mild disease, such as stage 0 or stage 1 fibrosis, can be observed but those with more advanced disease should be treated unless they have decompensated liver function. Starting treatment with peginterferon and ribavirin without performing liver biopsy can be considered in certain patients, particularly if they have no contraindications to treatment or if they have hepatitis C genotype 2 or 3. Reevaluation in 6 months would not provide any information that is not already available. Because the patient's depression seems reasonably well controlled, psychiatry consultation is not necessary. Psychiatry consultation can be considered for patients whose depression is not well controlled.

22. Answer d

This man is being treated for hepatitis C genotype 1. Treatment is with standard doses of peginterferon and ribavirin, and, after 12 weeks, he has had a one-log (tenfold) decrease in treatment. Patients who have less than a two-log decline at 12 weeks of treatment are unlikely to have a response to therapy, and discontinuing therapy is advised. This patient is more resistant to therapy because of his genotype 1 and perhaps his increased body mass index. Continuing therapy for an additional 12 weeks, increasing the peginterferon dose, or increasing the ribavirin is very unlikely to increase the chance of a response and is not part of standard care.

23. Answer b

This patient has hepatitis C genotype 1, with stage III disease. After 6 months of full-dose peginterferon and ribavirin, his HCV RNA remains positive. Because this patient will not have a response to therapy, treatment should be discontinued. Continuing therapy for 3 more months might reduce the HCV RNA level, but it is exceedingly unlikely to make him HCV RNA negative and even more unlikely to provide a sustained response. Adding ursodiol to the regimen has no role in the treatment of hepatitis C. Maintenance therapy with peginterferon has not been shown to be beneficial.

24. Answer c

This patient has hepatitis C genotype 2 and no features of advanced disease. It is likely that she has had hepatitis C for only 10 years. Because the likelihood is very high that this patient will have a response, treatment would be advised. Liver biopsy is not likely to change the management of this patient. Liver biopsy might change management only if she has cirrhosis, and this is very unlikely because of the short duration of hepatitis C. Observation could be considered if she has contraindications to therapy, but response rates are so high for hepatitis C genotype 2 that treatment generally is advised. Reassessment in 3 months would not change management.

25. Answer a

This patient has hepatitis C and symptoms consistent with vasculitis. This is likely a case of cryoglobulinemia. Patients with cryoglobulinemia nearly always have a positive rheumatoid factor test. The vasculitic rash typically improves with treatment of hepatitis C. Oral corticosteroids can be effective for the rash but usually are reserved for severe disease that does not respond to hepatitis C treatment. Polyarteritis nodosa typically complicates hepatitis B, not hepatitis C. Rheumatology consultation could be considered, but it generally is not necessary for patients with the usual clinical features of the disease.

26. Answer c

This patient presents with fulminant liver failure. Laboratory tests and copper studies are consistent with Wilson's disease. Patients with fulminant Wilson's disease should be given decoppering agents, but the likelihood of avoiding liver transplantation is so low that proceeding with immediate

transplantation is advised. This patient would be high priority and likely receive a liver relatively soon. Intracranial pressure monitoring is used by some groups but probably is not necessary at this point. Liver biopsy would only confirm the diagnosis of Wilson's disease and not change clinical management.

27. Answer a

This patient has anasarca and laboratory test abnormalities that confirm anemia, hypoalbuminemia, hypercalcemia, and renal insufficiency with proteinuria. The liver tests are notable for the high level of alkaline phosphatase. This constellation of symptoms and laboratory abnormalities should raise the possibility of an infiltrative liver disease. Because multiple myeloma with amyloidosis would be a strong consideration, serum protein electrophoresis should be the next test. Liver biopsy can confirm amyloidosis but would be more invasive than serum protein electrophoresis, with or without bone marrow biopsy. Knowing the angiotensin-converting enzyme level can be useful in diagnosing granulomatous diseases such as sarcoidosis, which can cause a high level of alkaline phosphatase. However, sarcoidosis would not account for the other clinical features. MRCP is not necessary because a biliary obstruction would not explain the other clinical features such as anemia and hypoproteinemia. Typically, hepatitis B would cause a greater increase in aminotransferase levels than in the alkaline phosphatase level.

28. Answer e

This patient has excessive alcohol intake and strong clinical evidence of cirrhosis. Biochemical features such as an AST level more than twice the ALT level is consistent with alcoholic hepatitis; however, the patient also has hepatitis C. Cessation of alcohol should produce clinical improvement. This patient, who almost certainly has cirrhosis, should undergo surveillance for hepatocellular carcinoma with periodic ultrasonographic examinations. Peginterferon and ribavirin would be a consideration for treating the hepatitis C but should not be prescribed for a patient who currently drinks alcohol in excess, particularly with evidence of alcoholic hepatitis and marked thrombocytopenia. Liver biopsy is not necessary for patients with a clear underlying cause of liver disease and clinical evidence of cirrhosis, as in this patient. Splenectomy should be avoided in patients with liver disease because of the high rate of operative morbidity and mortality. The patient is asymptomatic from the standpoint of gallstones; thus, cholecystectomy is not advised.

29. Answer d

Causes for indirect hyperbilirubinemia include Gilbert's syndrome, hemolysis, and cirrhosis. For this patient, Gilbert's syndrome is the most likely cause. Metastatic adenocarcinoma to the liver is a consideration in a patient with a history of colon cancer but that would be exceedingly unusual 8 years after colon cancer surgery. Also, the patient has normal ultrasonographic findings. Primary sclerosing cholangitis can cause an increased bilirubin level, but it should be a direct hyperbilirubinemia, and it is nearly always accompanied by a high level of alkaline phosphatase. Hepatitis C would typically have high aminotransferase levels. The patient is at increased risk for adenocarcinoma of the ampulla of Vater, but there is no evidence of bile duct obstruction and the alkaline phosphatase level is normal.

30. Answer b

This patient with a history of excess alcohol intake has evidence of encephalopathy and very high aminotransferase levels. The most common causes of aminotransferase levels of more than 5,000 U/L are acetaminophen hepatotoxicity, hepatic ischemia, and an unusual virus such as herpes. In this clinical situation, the cause is likely acetaminophen hepatotoxicity, particularly in an alcoholic patient in whom toxicity occurs with lower doses of acetaminophen than it does in a nonalcoholic patient. *N*-acetylcysteine should be administered regardless of the acetaminophen level. Pentoxifylline or corticosteroids can be considered for patients who have acute alcoholic hepatitis. Alcoholic hepatitis causes an increase in aminotransferase levels, but nearly always less than 400 U/L. Liver biopsy would not add to the clinical impression. Acyclovir could be considered for herpes hepatitis. Herpes hepatitis is characterized by very high aminotransferase levels, changes in mental status, and fever. The increased

bilirubin level and the absence of high fever would make herpes hepatitis unlikely; thus, acyclovir is not necessary.

31. Answer a

Modest abnormalities on liver tests are commonly seen after initiation of treatment with statin drugs. These modest abnormalities are nearly always transient and attributed to a period of adaptation. Observation would be reasonable. The decision to stop a potentially offending hepatotoxin usually is made when the aminotransferase levels are more than five times the upper limit of normal. Liver biopsy is not necessary because the liver enzyme abnormalities are only modest, but it can be considered if follow-up continues to show increased liver enzyme levels. Liver ultrasonography can be deferred until there is more evidence of chronic liver disease. The patient could have nonalcoholic fatty liver disease, but knowing this would not change management at this time. At this point, it is not necessary to stop atorvastatin therapy. Evaluation for other causes of chronic liver disease should be deferred until evidence of chronic liver injury is obtained.

32. Answer a

This patient has jaundice and a history of exposure to amoxicillin-clavulanate. Laboratory evidence is consistent with cholestasis, and ultrasonography does not show dilated bile ducts. The most likely cause in this case is liver injury due to amoxicillin-clavulanate. This is commonly a cholestatic injury. It typically occurs in older men, and symptoms frequently start after a course of the drug has already been completed. Resolution may take weeks. The best course would be to observe and follow the patient's laboratory test results. Liver biopsy is likely to demonstrate cholestasis and would not add to the decision for observation. CT could be considered if there were more suggestion of biliary obstruction and if a potential cause needed to be excluded. Testing for antimitochondrial antibody to diagnose primary biliary cirrhosis would be a consideration if the patient's laboratory test results do not improve. Primary biliary cirrhosis is more common in women. MRCP can be considered to help exclude biliary obstruction, but the patient has had two ultrasonographic studies that did not show evidence of a dilated bile duct; therefore, biliary obstruction is not likely.

33. Answer b

This patient has clinical acute hepatitis with fatigue and a high level of ALT. She has a history of hypothyroidism, and her medications include nitrofurantoin. She does have autoimmune markers and hypergammaglobulinemia. The most likely diagnoses would include nitrofurantoin-induced liver disease and autoimmune hepatitis. Nitrofurantoin can produce hepatotoxicity that can mimic autoimmune disease. Other drugs that can produce hepatotoxicity that mimicks autoimmune hepatitis include minocycline and α-methyldopa. Because the patient was exposed to a drug that can cause liver disease, the most likely diagnosis is nitrofurantoin-induced liver disease. This typically occurs in women who have a history of autoimmune disorders such as hypothyroidism. Unlike other causes of drug-induced liver disease, a drug-induced autoimmune disease can appear many months after the initiation of treatment with the offending medication. Estrogen is a rare cause of abnormal liver tests and typically produces cholestatic liver injury. Choledocholithiasis can result in an acute increase in aminotransferase levels, but patients usually have abdominal pain. Primary biliary cirrhosis would produce a cholestatic rather than a hepatitic liver enzyme profile.

34. Answer b

This patient has sudden onset of ascites and a background history of ulcerative colitis that is well controlled with azathioprine and mesalamine. The liver enzyme levels are minimally increased in a relatively nonspecific pattern. Ultrasonography shows ascites and patent hepatic and portal veins. In a patient with acute onset of ascites, the obstruction of hepatic venous outflow needs to be considered. With this history and patent hepatic veins seen on ultrasonography, the most likely diagnosis is sinusoidal obstruction syndrome or veno-occlusive disease. Although this occurs most commonly after bone marrow transplantation, it can be seen also with azathioprine therapy, which is likely the culprit here. Primary sclerosing cholangitis could produce a cholestatic liver enzyme profile or advanced liver disease but

would be an unlikely cause of acute onset of ascites. Right-sided heart failure is less likely in a young man without any history of cardiac disease. Mesalamine-induced liver disease is rare and typically would produce higher levels of liver enzymes without ascites.

35. Answer c

This patient has abnormal iron tests and is homozygous for hereditary hemochromatosis. Phlebotomy would be advised. Liver biopsy is necessary only if the ferritin level is more than 1,000 μg/L or liver enzyme levels are abnormal. Alcohol excess can produce abnormal iron tests, but the patient's consumption is not excessive.

36. Answer d

The patient has hepatitis C genotype 2. She has clinical evidence of cirrhosis but also has slightly abnormal iron tests with an increased ferritin level but normal percent saturation. The most likely diagnosis is hepatitis C, and because of genotype 2 and evidence of advanced disease, treatment would be recommended. The increased iron values almost certainly are due to hepatitis C. It would be very unusual for a patient with hereditary hemochromatosis to have a normal percent saturation, so *HFE* gene testing is not necessary. Liver biopsy is not necessary because of the evidence of cirrhosis. Phlebotomy does not seem to affect the effectiveness of treatment of hepatitis C and would not be advised.

37. Answer c

The patient has clinical and biochemical evidence of iron overload disease. He has no clinical features of advanced liver disease, and *HFE* gene test findings are unremarkable. Despite the negative *HFE* gene test, the likely diagnosis is hereditary hemochromatosis. Confirmation would be advised. Magnetic resonance imaging could be considered, but this is still an investigational tool. Because of the high ferritin level, it would be advisable to exclude cirrhosis; thus, a liver biopsy both for a standard histologic study and quantification of iron would be the next test. Therapeutic phlebotomy will likely be advised but should be reserved until a firm diagnosis is made on the basis of the liver biopsy study and iron quantification.

38. Answer c

This young man has abnormal liver tests and a low level of ceruloplasmin. In this situation, Wilson's disease needs to be excluded. The best next test would be a slit-lamp examination to search for Kayser-Fleischer rings. Their presence would be essentially diagnostic of Wilson's disease in this clinical setting. Rarely, Kayser-Fleischer rings can occur in patients with cholestatic diseases such as primary biliary cirrhosis, but this is very unlikely in this clinical situation. Liver biopsy with copper quantification can also help diagnose Wilson's disease, but it is more invasive than a slit-lamp examination. Even if the patient's liver test results improve with weight loss, Wilson's disease needs to be excluded because of the low ceruloplasmin level. A serum free copper level can be helpful in the setting of Wilson's disease, but normal values do not exclude the diagnosis. Treatment with penicillamine should be initiated only after the diagnosis has been confirmed.

39. Answer a

The patient has a mild increase in liver enzyme levels, both AST and ALT levels. She has a history of dermatomyositis, which is controlled with prednisone. The normal creatine kinase and aldolase levels mean that the increased aminotransferase levels almost certainly are of hepatic origin. Because of the history of alcohol excess, the most likely diagnosis is alcoholic liver disease. Nonalcoholic fatty liver disease cannot be diagnosed in a woman with this degree of alcohol consumption. Also, she does not have other clinical features consistent with nonalcoholic fatty liver disease. Celiac disease is also a consideration, but it is much less common than alcoholic liver disease. Autoimmune hepatitis would typically produce higher aminotransferase levels, with the ALT level higher than the AST level.

40. Answer a

The patient has hereditary hemochromatosis. The diagnosis is essentially confirmed because of abnormal iron test results, homozygosity for C282Y, and the absence for any other cause of liver disease. Even though liver biopsy is not needed for diagnosis, it would be recommended to exclude cirrhosis in this man with a ferritin level greater

than 1,000 μg/L. Although the presence of cirrhosis would not alter plans for phlebotomy, it would mandate screening for hepatocellular carcinoma. The amount of alcohol that the patient drinks should not cause abnormal iron test results, although this certainly should be curtailed in the setting of another cause for liver disease. Magnetic resonance imaging of the liver can help diagnose iron overload but is still an investigational tool.

41. Answer d

The patient has evidence of sclerosing cholangitis, with a prominent distal bile duct stricture. Although this may represent primary sclerosing cholangitis, the patient does not have inflammatory bowel disease, and IgG4-associated cholangitis should be excluded. Therefore, the best next test would be to determine the serum IgG4 level. Should IgG4-associated cholangitis be confirmed, treatment with corticosteroids would be advised. MRCP, ERCP, and endoscopic ultrasonography are not necessary at this point unless the lack of another diagnosis is forthcoming. These studies would be especially useful if biliary malignancy was a concern. Antimitochondrial antibody would be useful to diagnose primary biliary cirrhosis, a disease that does not produce abnormal ERCP findings.

42. Answer c

The patient has HIV infection and hepatitis C. Currently, the HIV infection is minimally active, with a viral level that is low and a CD4 count that is reasonably high. In this unusual situation, the best option for this patient with relatively advanced stage hepatitis C would be the introduction of treatment with pegylated interferon. Antiretroviral therapy usually would be initiated first but is not necessary in this patient with controlled HIV disease. One rationale for treating the hepatitis C first is to decrease the risk of hepatotoxicity from antiretroviral therapy that occurs in patients with hepatitis C.

43. Answer a

The patient's AST level is increasing, and ultrasonography shows changes in liver echogenicity consistent with fat. Although this disorder usually is merely nonalcoholic fatty liver disease associated with metabolic syndrome, the increasing AST level would be a bit unusual, and one of the drugs that can cause this effect is tamoxifen. Discontinuation of tamoxifen therapy with consideration of an alternative agent would be advised. Liver biopsy could be considered, but it would be best to wait until after a trial to see if the liver enzyme values improve after tamoxifen therapy has been stopped. Liver biopsy is likely to show steatohepatitis but will not differentiate the specific cause. Weight loss with repeat liver tests is a consideration, but the patient is not excessively overweight. CT of the liver would not add much information to that obtained from ultrasonography. The amount of alcohol the patient consumes would not cause liver disease.

Section VII

Pancreas and Biliary Tree

CHAPTER 35

Acute Pancreatitis

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Approximately 210,000 new cases of acute pancreatitis occur annually in the United States, and its incidence is increasing in and outside this country. Of the new cases, about 80% are the interstitial (edematous) variety and the other 20% are the necrotizing variety. Necrotizing pancreatitis accounts for most of the morbidity and nearly all the mortality associated with acute pancreatitis.

ETIOLOGY

Gallstones and alcohol are the most common causes of acute pancreatitis in the United States (Table 1). Gallstones are the most common cause in affluent populations and alcohol is in lower socioeconomic populations. Other causes include hyperlipidemia, hypercalcemia, medications (Table 2), trauma, postoperative state, infections by various agents, and endoscopic retrograde cholangiopancreatography (ERCP). About 20% of cases of acute pancreatitis are classified as "idiopathic" because no cause is found even after extensive testing. Debated causes of acute pancreatitis are sphincter of Oddi dysfunction and pancreas divisum.

Gallstones are thought to produce acute pancreatitis because they pass into the common bile duct and obstruct the channel shared by the bile duct and pancreatic duct. Patients with gallstone pancreatitis frequently have abnormal liver enzyme levels.

Pathology

The two forms of acute pancreatitis defined by inflammatory changes in the pancreatic parenchyma are *interstitial* and *necrotizing*. In interstitial pancreatitis, edema and inflammation of the pancreatic parenchyma occur without death of pancreatic acini. In necrotizing pancreatitis, there is extensive parenchymal destruction, frequently with peripancreatic fat necrosis.

CLINICAL PRESENTATION

The clinical presentation of acute pancreatitis ranges from mild, nonspecific epigastric pain to a catastrophic acute medical illness. Occasionally, pain may not be present (especially in the case of postoperative acute pancreatitis following kidney transplant or cardiac surgery), and sometimes

Abbreviations: APACHE, acute physiology and chronic health evaluation; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography.

Table 1. Causes of Acute Pancreatitis

Most common
Choledocholithiasis
Ethanol
Idiopathic
Less common
Endoscopic retrograde cholangiopancreatography (especially for suspected sphincter of Oddi dysfunction)
Pancreatic ductal obstruction (pancreatic carcinoma, intraductal mucinous papillary tumor)
Hyperlipidemia (types I, IV, and V)
Hypercalcemia
Drugs (see Table 2)
Pancreas divisum (?)
Abdominal trauma
Least common
Viral infection
Parasitic infestation of pancreatic duct
Hereditary (familial)

Modified from Baron TH, Morgan DE: Acute necrotizing pancreatitis. N Engl J Med. 1999;340:1412-7. Used with permission.

Table 2. Drugs Associated With Acute Pancreatitis

Likely association	Possible association
α-Methyldopa	Amiodarone
Asparaginase	Ampicillin
Azathioprine	Anticholinesterases
Cimetidine	Carbamazepine
2′,3′-Dideoxycytidine	Cisplatin
2′,3′-Dideoxyinosine	Colchicine
Estrogens	Corticosteroids
Furosemide	Cyclosporine
6-Mercaptopurine	Cytarabine
Metronidazole	Delavirdine
Pentamidine	Diazoxide
Salicylates	Diphenoxylate
Sulfasalazine	Enalapril
Sulfonamides	Ergotamine
Sulindac	Erythromycin
Tetracyclines	Ethacrynic acid
Valproic acid	Ganciclovir
	Gold compounds
	Indinavir
	Interleukin-2
	Isotretinoin
	Ketoprofen
	Lisinopril
	Mefenamic acid
	Metolazone
	Nelfinavir
	Nevirapine
	Nitrofurantoin
	Octreotide
	Oxyphenbutazone
	Paracetamol (acetaminophen USP)
	Phenformin
	Phenolphthalein
	Piroxicam
	Procainamide
	Ranitidine
	Ritonavir
	Roxithromycin
	Stavudine
	Tretinoin
	Tryptophan

acute pancreatitis is diagnosed only at autopsy. Patients with interstitial acute pancreatitis have a clinically mild presentation.

Patients usually present with epigastric or left upper quadrant pain that may radiate to the back. Nausea and vomiting are nearly always present. In the severe form, the patient is systemically ill with fever, tachycardia, tachypnea, and hypotension. Although the findings of ecchymoses in the periumbilical area (Cullen sign) or on the flanks (Grey Turner sign) have received much attention, they are uncommon.

The differential diagnosis of acute pancreatitis is broad and includes myocardial infarction, peptic ulcer disease, symptomatic cholelithiasis, and small-bowel ischemia.

SEVERITY STRATIFICATION

Several severity-of-illness classifications for acute pancreatitis are used to identify patients at risk for the development of complications. The Ranson

score consists of 11 clinical signs with prognostic significance: 5 criteria are measured at the time of admission, and 6 criteria are measured between admission and 48 hours later (Table 3). The number of Ranson signs and the incidence of systemic complications and presence of pancreatic necrosis are correlated. The Acute Physiology and Chronic Health Evaluation (APACHE) II score is a grading system based on 12 physiologic variables, patient age, and previous history of severe organ system insufficiency or immunocompromised state (Table 4). It allows stratification of the severity of illness on admission and may be recalculated daily. The main disadvantage of the Ranson score is that it may not be completed until 48 hours after admission. The APACHE II scoring system has the advantage of being completed at the initial presentation as well as being repeated daily, but it is cumbersome to use.

The Atlanta classification is the most widely used clinical system for indicating the severity of acute pancreatitis. This classification recognizes *mild* and *severe* types of the disease, which are synonymous with the interstitial and necrotizing types, respectively. It classifies an attack of acute pancreatitis as severe if any of the following criteria are met: 1) organ failure with one or more 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), and gastrointestinal tract bleeding (>500 mL in 24 hours); 2) local complications such as pseudocyst, abscess, or pancreatic necrosis; 3) three or more Ranson criteria; or 4) eight or more APACHE II criteria. Terms such as phlegmon, hemorrhagic pancreatitis, infected pseudocyst, and persistent pancreatitis were omitted because of the confusion they caused.

Various biochemical markers used to predict the severity of acute pancreatitis have been evaluated. The "gold standard" for predicting the severity of acute pancreatitis is C-reactive protein, and a value greater than 150 mg/L is considered diagnostic of severe acute pancreatitis when obtained 48 hours after the onset of symptoms. Other potential predictive markers of severity being evaluated include hemoconcentration with an admission hematocrit of 44 or more, serum trypsinogen activation peptide, polymorphonuclear elastase, carboxypeptidase activation peptide, interleukin-6, interleukin-8, and procalcitonin.

Table 3. Ranson Criteria of Severity

At admission	During initial 48 hours
Age >55 years	Hematocrit decreases >10%
Leukocytes >16 × 10^9/L	Blood urea nitrogen increases >5 mg/dL
Blood glucose >200 mg/dL	Serum calcium <8 mg/dL
Serum lactate dehydrogenase >350 IU/L	Arterial PaO_2 <60 mm Hg
Serum aspartate aminotransferase >250 IU/L	Base deficit >4 mEq/L
	Fluid sequestration >6 L

Modified from Banks PA. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 1997;92:377-86. Used with permission.

LABORATORY FINDINGS

The diagnosis of acute pancreatitis requires one of the following criteria: a serum level of amylase or lipase 3 times or more the upper limit of normal for that particular laboratory assay, definite findings on abdominal ultrasonography or computed tomography (CT), or surgical or autopsy confirmation.

The two major pitfalls of the serum amylase assay are 1) it is a sensitive but not specific test and 2) various intra-abdominal diseases included in the differential diagnosis of acute pancreatitis may cause an increase in the serum level of amylase. Another problem is the falsely low serum amylase level in hyperlipidemia. Although the serum lipase assay was developed in an attempt to have a more specific test, it does not appear to have a significantly better sensitivity and specificity.

A threefold or more increase in the serum alanine aminotransferase level suggests a biliary origin of acute pancreatitis. A fasting triglyceride value of more than 1,000 mg/dL or a persistent increase after the attack has resolved suggests hyperlipidemia as the cause and not the effect of acute pancreatitis. It is

Table 4. APACHE II Scoring System*

Physiology points	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/minute	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate, breaths/minute	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (kPa)†									
FIO_2 ≥50% A-aDO_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, μmol/L	≥300	171-299		121-170	50-120		<50		
Packed cell volume, %	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White blood cell count, × 10^9/L	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1

**APACHE II score = acute physiology score + age points + chronic health points.*

†If fraction of inspired oxygen (FIO_2) is ≥50%, the alveolar-arterial gradient (A-a) is assigned points. If fraction of inspired oxygen is <50%, partial pressure of oxygen is assigned points.

Other points

Glasgow coma scale: score is subtracted from 15 to obtain points.

Age <45 years = 0 points, 45-54 = 2, 55-64 = 3, 65-75 = 5, >75 = 6.

Chronic health points (must be present before hospital admission): 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; immunosuppression—eg, radiation, chemotherapy, recent or long-term high-dose corticosteroid therapy, leukemia, acquired immunodeficiency syndrome. 5 points for emergency surgery or nonsurgical patient, 2 points for elective surgical patient.

Modified from Banks PA. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 1997;92:377-86. Used with permission.

important to measure the serum level of calcium after the attack has resolved because the levels can be spuriously low during an attack and hypercalcemia as the cause of acute pancreatitis can be missed.

The serum levels of creatinine and glucose may be increased. Decreases in total serum calcium more likely are related to low serum levels of albumin than to true hypocalcemia, which is reflected in measurements of ionized calcium. Also, hypoxemia may be present.

ABDOMINAL IMAGING STUDIES

In acute pancreatitis, plain abdominal radiographs are frequently normal, 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. The 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.

If the diagnosis is in doubt, the best imaging study is abdominal CT. It is imperative that intravenous contrast be administered unless there is a major contraindication. Pancreatic perfusion is disrupted in the case of pancreatic necrosis and is detectable only if intravenous contrast is given (Fig. 1 and 2). A CT classification system for the severity of acute pancreatitis has been developed on the basis of the degree of necrosis and number of fluid collections. High mortality can be expected if the CT severity index of Balthazar is 7 or more. Patients with acute pancreatitis who have normal CT findings have a good prognosis. The correlation is good 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.

It is not absolutely necessary to obtain abdominal imaging studies at presentation of acute pancreatitis unless the diagnosis is in doubt. If the diagnosis is in doubt, contrast-enhanced CT rather than ultrasonography should be performed. If the cause is in doubt, ultrasonography is the best test to confirm gallstones. In definite cases of acute pancreatitis, contrast-enhanced CT can be performed after 3 days if the patient is not responding or earlier if the patient's condition is deteriorating. Recently, magnetic resonance imaging has been compared prospectively with CT in the setting of severe pancreatitis and found to be a reliable method for staging severity, to have predictive value for the prognosis of the disease, and to have fewer contraindications than CT. It also can detect disruption of the pancreatic duct, which may occur early in the course of acute pancreatitis.

TREATMENT

Because the prognosis of interstitial pancreatitis is different from that of necrotizing pancreatitis, management of the two is discussed separately.

Treatment of Interstitial Acute Pancreatitis

Patients with interstitial pancreatitis may be managed on a general hospital ward, without need for intensive care monitoring. Often, all that is needed is to withhold oral intake and liberally administer intravenous fluids and analgesics. Nasogastric tubes should not be used routinely because they do not improve disease outcome and add to patient discomfort. However, for patients with exceptional nausea and vomiting and ileus, a nasogastric tube may help relieve the symptoms. Empiric use of antibiotics should be avoided in interstitial pancreatitis because these agents do not alter the outcome.

If laboratory findings (increased levels of aminotransferases or bilirubin or both) and ultrasonography indicate that gallstones are the cause of the pancreatitis, cholecystectomy should be performed before hospital dismissal to prevent recurrent attacks of acute pancreatitis. 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 demonstrates only sludge or small stones.

If the cause of pancreatitis is in doubt, the serum levels of lipids should be determined and drugs that may have caused acute pancreatitis should be reviewed thoroughly. In addition,

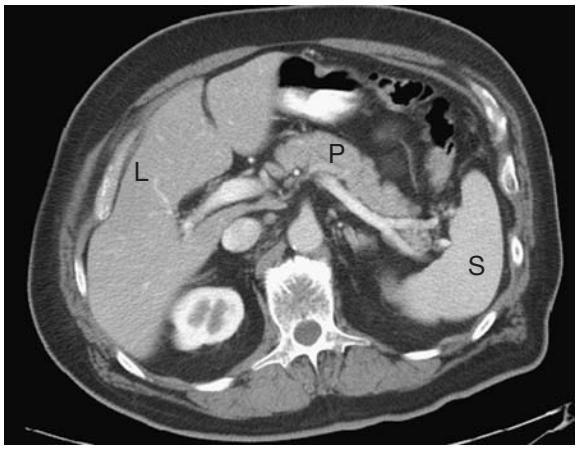

Fig. 1. Normal contrast-enhanced computed tomogram of the pancreas. Note that the pancreas (P) has a uniform enhancement intermediate between that of the liver (L) and spleen (S).

abdominal ultrasonography should be performed. After this, if the cause is still in doubt, abdominal CT should be performed to exclude anatomical causes of pancreatic ductal obstruction, such as a pancreatic or ampullary mass lesion, or suggestion of intraductal mucinous papillary tumor, especially in patients older than 50 years. For elderly patients,

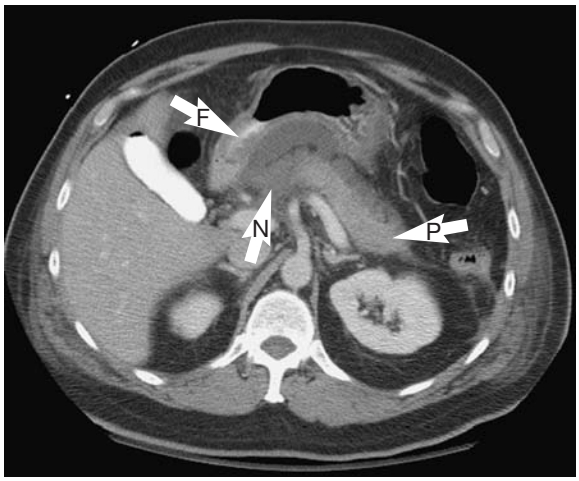

Fig. 2. Acute necrotizing pancreatitis. The patient had severe pancreatitis after endoscopic retrograde cholangiopancreatography. Note fluid collection (*arrowhead F*) near the neck of the pancreas. The density of the necrotic portion of the pancreas (*arrowhead N*) is less than that of the normal-enhancing pancreas in the tail (*arrowhead P*).

endoscopic ultrasonography, magnetic resonance cholangiopancreatography, or ERCP should be considered if the CT findings are negative.

Treatment of Acute Necrotizing Pancreatitis

Supportive Care

The management of patients with clinically severe pancreatitis due to pancreatic necrosis is different from that for patients with interstitial pancreatitis. Aggressive hydration with intravenous fluids is very important. Patient-controlled analgesia for pain control requires fentanyl or morphine. Although animal experiments indicated that morphine caused spasm of the sphincter of Oddi, there is no definite human evidence that morphine worsens the disease. Patients should be placed in the intensive care unit. In recent years, the management of these patients has shifted from early surgical débridement (necrosectomy) to aggressive intensive medical care. Aggressive medical management, with emphasis on the prevention of infection, has allowed the prompt identification of complications and improvement in outcome for these patients.

Early mortality (within the first 1 or 2 weeks) is due to multisystem organ failure resulting from systemic inflammatory response syndrome. 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.

Antibiotics

The prevention of infection is critical because infected necrosis develops in 30% to 70% of patients with acute necrotizing pancreatitis and accounts for more than 80% of deaths due to acute pancreatitis. Early studies on antibiotic therapy for patients with acute pancreatitis failed to demonstrate an important benefit because these studies included both patients with interstitial-edematous acute pancreatitis and patients with necrotizing acute pancreatitis. In experimental acute necrotizing pancreatitis, pancreatic infection occurs primarily as a result of bacterial translocation from the colon. Human studies have shown benefits from systemic

antibiotic therapy and *selective gut decontamination*. In a prospective trial involving a group of patients with necrotizing pancreatitis, a significant decrease in gram-negative pancreatic infection and late mortality (more than 2 weeks after the onset of pancreatitis) was found in the selective gut decontamination group. Because selective gut decontamination antibiotics must be administered orally and rectally, this regimen may pose problems from a nursing standpoint and has not been adopted. The more commonly used approach is systemic administration of antibiotics to prevent pancreatic infection.

Prospective and retrospective studies have shown a significant decrease in pancreatic infection in patients given imipenem-cilastatin (Primaxin) intravenously, although a decrease in mortality rate was not demonstrated. Fluoroquinolones should offer excellent protection against infection of necrosis. However, the results from two randomized prospective trials of quinolone regimens for patients with severe pancreatitis suggest that these agents are not effective prophylaxis for reducing the infectious complications of acute pancreatitis. In a recently published *Cochrane Database Systematic Review* of four prospective randomized trials in which antibacterial therapy was evaluated in patients with severe acute pancreatitis associated with pancreatic necrosis proven by intravenous contrast-enhanced CT, there was strong evidence that intravenous antibiotic prophylactic therapy for 10 to 14 days decreased the risk of superinfection of necrotic tissue and mortality. Currently, prophylaxis with intravenously administered antibiotics that have excellent penetration of pancreatic tissue (imipenem-cilastatin) is recommended. A concern with prophylactic antibiotics for severe acute pancreatitis is the development of fungal superinfection. Strategies that have been proposed to limit this complication include antibiotic therapy limited to 7 days or prophylactic therapy with antifungal drugs. These need to be studied in future trials. Therapy should begin as soon as severe acute pancreatitis is diagnosed. Recently, a second antibiotic (meropenem) in the same class has been shown to be equally effective for preventing septic complications of severe acute pancreatitis. Additional studies are needed to determine which subgroups of severe acute pancreatitis will benefit from prophylactic antibiotic therapy.

Detection of Pancreatic Infection

Although sterile and infected acute necrotizing pancreatitis can be difficult to distinguish clinically because both may produce fever, leukocytosis, and severe abdominal pain, the distinction is important. Without intervention, the mortality rate for patients with infected acute necrotizing pancreatitis is nearly 100%. The bacteriologic status of the pancreas may be determined with CT-guided fine-needle aspiration of pancreatic and peripancreatic tissue or fluid. This aspiration method is safe, accurate (sensitivity of 96% and specificity of 99%), and recommended for patients with acute necrotizing pancreatitis whose condition deteriorates clinically or fails to improve despite aggressive supportive care. Ultrasonographically guided aspiration may have a lower sensitivity and specificity, but it can be performed at the bedside. Surveillance aspiration may be repeated on a weekly basis as indicated clinically.

Role of Endoscopic Retrograde Cholangiopancreatography

ERCP with biliary sphincterotomy may improve the outcome of patients who have severe gallstone pancreatitis. Initial studies in which urgent ERCP (within 72 hours after admission) and biliary sphincterotomy were performed in patients with acute gallstone pancreatitis and choledocholithiasis showed improved outcome for only the group of patients presenting with clinically severe acute pancreatitis. The improvement was attributed to relief from pancreatic ductal obstruction produced by an impacted gallstone in the common biliary-pancreatic channel of the ampulla of Vater. More recent studies have suggested that improved outcome after ERCP and sphincterotomy in gallstone pancreatitis may be the result of reduced biliary sepsis rather than a true improvement in pancreatitis. Therefore, for patients with severe gallstone acute pancreatitis, ERCP should be reserved for those with biliary obstruction suspected on the basis of hyperbilirubinemia and clinical cholangitis.

Nutritional Support for Acute Necrotizing Pancreatitis

To meet increased metabolic demands and to "rest" the pancreas, total parenteral nutrition has been used frequently for nutritional support of patients with acute necrotizing pancreatitis, but it does not

hasten the resolution of acute pancreatitis. In randomized prospective studies of severe acute pancreatitis that compared total parenteral nutrition with enteral feeding (through a nasoenteric feeding tube placed under radiographic guidance beyond the ligament of Treitz), patients who received enteral feeding had significantly fewer total and infectious complications, a threefold decrease in the cost of nutritional support, and improvement in acute phase response and disease severity scores. A recent meta-analysis of enteral and parenteral nutrition in patients with acute pancreatitis found that enteral nutrition was associated with a significantly lower incidence of infections, reduced number of surgical interventions to control pancreatitis, and a decreased length of hospital stay. The two groups of patients had no significant differences in mortality or noninfectious complications. It appears that this form of enteral feeding is preferable for patients who have acute necrotizing pancreatitis but not severe ileus. Possibly, nasogastric feeding may be as safe, too, as indicated by a small randomized study that compared nasogastric feeding with nasojejunal feeding.

Surgical Therapy for Pancreatic Necrosis

The timing and type of pancreatic intervention for acute necrotizing pancreatitis are debated, although guidelines from the International Association of Pancreatology for the Surgical Management of Acute Pancreatitis have been published recently. Because the mortality rate of sterile acute necrotizing pancreatitis is approximately 10% and surgical intervention has not been shown to decrease this rate, nonsurgical therapy is recommended. Conversely, infected acute necrotizing pancreatitis is considered uniformly fatal without intervention. Aggressive surgical pancreatic débridement (necrosectomy) is the standard of care and may require multiple abdominal reexplorations. Necrosectomy should be performed soon after infected necrosis has been confirmed. Surgical débridement of sterile necrosis in patients with multisystem organ failure unresponsive to maximal treatment in an intensive care unit is considered an indication for surgery. However, delaying surgical intervention more than 14 days after the onset of acute necrotizing pancreatitis, when possible, is currently the recommendation, based on recent evidence. This is related to better demarcation between viable and necrotic tissue at the time of operation. The role of delayed necrosectomy (after multisystem organ failure has resolved) in sterile acute necrotizing pancreatitis is also debated. Some investigators advocate débridement in patients who are still systemically ill with fever, weight loss, intractable abdominal pain, inability to eat, and "failure to thrive" 4 to 6 weeks after the onset of acute pancreatitis. Others, however, argue that delayed necrosectomy is unnecessary as long as the process remains sterile. Frequently, multiple operations are required to remove the necrotic pancreatic and peripancreatic material. Abdominal zipper or open packing of the wound permits repeated explorations. If the necrosis is well contained and organized or if the patient is a poor surgical risk, minimal access necrosectomy, either by the percutaneous route with a nephroscope or the endoscopic route through the stomach, duodenum, or papilla, is the new approach. Pancreatic or gastrointestinal tract fistulae (or both) occur in up to 40% of patients after surgical necrosectomy and often require an additional procedure for closure. The mortality rate after necrosectomy for acute necrotizing pancreatitis is approximately 20%.

Prognosis

The overall mortality rate for severe acute pancreatitis has decreased as a result of improved intensive care unit therapies, antibiotics, and delay of surgery and is now approximately 15%. Mortality occurs in two phases: 1) early deaths (1-2 weeks after the onset of pancreatitis, approximately 50% of all deaths) are due to multisystem organ failure from the release of inflammatory mediators and cytokines and 2) late deaths result from local or systemic infections. As long as acute necrotizing pancreatitis remains sterile, the overall mortality rate is approximately 10%. The mortality rate at least triples 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.

Long-Term Sequelae of Acute Necrotizing Pancreatitis

Despite the enormous cost of caring for patients who have acute necrotizing pancreatitis, the mean

quality-of-life outcomes up to 2 years after treatment of pancreatic necrosis are similar to those for coronary artery bypass grafting. The long-term clinical endocrine and exocrine consequences of acute necrotizing pancreatitis appear to depend on several factors: the severity of necrosis, cause (alcoholic vs nonalcoholic), continued use of alcohol, and the degree of surgical pancreatic débridement. Sophisticated exocrine function studies have shown persistent functional 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. Follow-up pancreatography frequently shows obstruction, disruption, or disconnection of the pancreatic duct, which may result in persistence or recurrence of fluid collections. This may require endoscopic treatment or distal pancreatic resection.

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CHAPTER 36

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 presentation 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 eventual development of intraductal stones later in the disease course. Eventually, 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 organ distal to the obstruction. It generally is not associated with 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 is commonly seen distal to pancreatic tumors (ductal adenocarcinoma and intraductal papillary mucinous tumor [IPMT]) and postinflammatory strictures following acute or traumatic pancreatitis.

Chronic autoimmune pancreatitis is a unique form of chronic pancreatitis that can be defined as a systemic fibroinflammatory disease that afflicts not only the pancreas but also various other organs, including the bile duct, salivary glands, retroperitoneum, and lymph nodes. Organs affected by autoimmune pancreatitis have a lymphoplasmacytic infiltrate rich in IgG4-positive cells. The inflammatory process responds to corticosteroid therapy. The most common presentation of this form of chronic pancreatitis is with obstructive jaundice, and it rarely presents with clinically acute pancreatitis. Pancreatic calcification is not common. It is thought to be a systemic autoimmune disorder; its best known serologic marker is an increased level of IgG4.

The rest of the discussion in this chapter is related to chronic calcifying pancreatitis.

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; IPMT, intraductal papillary mucinous tumor; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

Several conditions are associated with chronic calcifying pancreatitis (Table 1). The pathogenesis of chronic pancreatitis due to these presumed etiologic agents is largely unknown. In the West, the most common cause of chronic calcifying pancreatitis is chronic alcohol abuse.

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

Computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP) are the imaging procedures commonly used to evaluate for structural changes in the pancreas. 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 with possible chronic pancreatitis.

Table 1. Causes of Chronic Calcifying Pancreatitis (CP)

Presumed cause	Salient features
Alcohol	Commonest cause of CP in the West About 5% of alcoholics develop CP, usually after long history of alcohol abuse
Hereditary	Mutations in cationic trypsinogen gene (R117H, N21I) associated with high penetrance (80%) autosomonal dominant form of CP Presents at an early age (first and second decades) High risk of pancreatic cancer with time, especially in 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 associated with mutations in *CFTR* gene, *SPINK1* gene, and some other mutations in cationic trypsinogen also associated with CP (probably disease modifiers) Pain is common feature of early-onset disease Senile form may be painless in ~50% of patients
Hypercalcemia	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

It is noninvasive, widely available, and has relatively good sensitivity for diagnosing moderate-to-severe chronic pancreatitis. The findings, however, can be normal in early chronic pancreatitis. Chronic pancreatitis is diagnosed on 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 good for the evaluation of pain in a patient with known chronic pancreatitis, because it can identify most complications of chronic pancreatitis, including peripancreatic fluid collections, bile duct obstruction, and bowel obstruction, and can reliably visualize inflammatory or neoplastic masses larger than 1 cm.

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 2. Minor changes in the ducts are hard to interpret and are subject to interobserver variation. False-positive results may be obtained in older patients who may have benign pancreatic duct changes without pancreatitis and in patients with recent acute pancreatitis who develop reversible or permanent pancreatic duct changes in the absence of chronic pancreatitis.

Diagnostic ERCP carries a small (2%-5%) risk 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. However, the role of EUS and the diagnostic criteria for diagnosing chronic pancreatitis with EUS are still being evaluated. Problems with interpretation may arise in older patients who have senile changes in the pancreas, in alcoholics in whom fibrosis may be present but not pancreatitis, and in patients who had a recent episode of acute pancreatitis. There is also the problem of interobserver variability in interpretation. Currently, the diagnosis of chronic pancreatitis should not be based on EUS criteria alone.

MRCP is noninvasive, avoids ionizing radiation and administration of contrast, and does not routinely require sedation, making it a diagnostic procedure of choice for some groups of patients. It 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.

Table 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

Functional Testing in the Evaluation of Chronic Pancreatitis

The pancreas has great functional reserve, so that 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 pancreatic function tests 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 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 the onset of pain is much lower (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 of the patients who have late-onset (senile) idiopathic chronic pancreatitis. Diabetes and calcification are uncommon at diagnosis in alcoholic pancreatitis, but they are present at diagnosis in more than 80% of patients with tropical pancreatitis.

In alcoholic chronic pancreatitis, death often is related to smoking and nonpancreatic and alcohol-related complications (especially cancers). In 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. The majority (85%) of patients, with or without resection, eventually develop diabetes, 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 come 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 USP 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 duct "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

This complication 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 secondary 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 with the pancreas, the vein is often affected by pancreatic inflammation or fibrosis. Patients with left-sided portal hypertension (or 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, our poor understanding of the pathogenesis of pain has made it difficult to manage rationally abdominal pain in chronic pancreatitis. Despite some optimism that pancreatic pain eventually "burns out," most clinicians agree that the pain may diminish but it 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, either in comparison 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 with 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 use 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. Currently, the evidence supporting the use of endoscopic therapy for pain in chronic pancreatitis is preliminary and confined largely to short-term focused observations. Although these procedures may hold promise, they need

to be evaluated further in clinical trials. Celiac plexus block appears to have limited benefit in chronic pancreatitis.

Surgical therapy is an option for patients who clearly appear to have 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, for patients with disease unresponsive to medical therapy and not suitable for other surgical options, total pancreatectomy. A recent randomized controlled trial comparing pancreaticojejunostomy and endoscopic therapy for chronic pancreatitis with dilated ducts showed that surgery provided superior results, with a higher proportion of patients reporting 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 with severe pain not responsive to lesser tactics.

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CHAPTER 37

Pancreatic Neoplasms

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Exocrine pancreatic neoplasms are of epithelial or nonepithelial origin (Table 1). Of all pancreatic tumors, ductal adenocarcinoma is the most important.

PANCREATIC DUCTAL ADENOCARCINOMA

Cancer of the pancreas is a fatal disease and an increasing health problem. In the United States, more than 32,000 persons die of pancreatic cancer annually. The overall survival rate with pancreatic cancer is less than 5%, the lowest 5-year survival rate of any cancer. This is due partly to the low resectability rate.

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 (Table 2).

Table 1. Exocrine Pancreatic Tumors

Epithelial
Cystic
Microcystic (serous) cystadenoma
Macrocystic (mucinous) cystadenoma
Intraductal papillary mucinous tumor
Solid-cystic (solid and papillary) tumor
Solid
Variants of ductal adenocarcinoma*
Adenosquamous, anaplastic, acinar cell
Nonepithelial
Connective tissue origin
Leiomyosarcoma
Liposarcoma
Rhabdomyosarcoma
Malignant neurolemmoma
Malignant lymphomas

*Most important.

Risk Factors for Development of Pancreatic Cancer

Early diagnosis of pancreatic cancer is difficult because the tumor frequently is detected at a late stage, and until recent years, risk factors for the development of pancreatic cancer were undefined. However, several risk factors have now been described.

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; 5-FU, 5-fluorouracil; MDCT, multidetector computed tomography; MRI, magnetic resonance imaging.

Table 2. Staging of Pancreatic Ductal Adenocarcinoma

Definition of TNM			
Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of 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		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Environmental Factors

Aromatic amines appear to be responsible for the increased risk of pancreatic cancer associated with environmental factors. Thus, 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 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. Furthermore, animal studies indicate that aromatic amines may cause pancreatic cancer.

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 likely is due to the duration of chronic pancreatitis rather than being related specifically to the gene mutation. The estimated cumulative risk of pancreatic cancer at age 70 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-to-expected cases) of 16. However, chronic pancreatitis is relatively uncommon and does not contribute significantly to the population of patients with pancreatic cancer.

Intraductal Papillary Mucinous Tumors (see "Cystic Pancreatic Tumors")

This disease was recognized first in Japan in 1982 and increasingly is 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.

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 of the

patients are insulin-dependent, and in some, diabetes is diagnosed at the same time as pancreatic cancer. The precise risk of pancreatic cancer in patients with new-onset diabetes is not well defined, but according to a meta-analysis, the risk of pancreatic cancer developing in patients who have had diabetes for more than 1 year is doubled.

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, which represents a 13-fold increase over controls. Families with two 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*), mismatch repair genes (*HNPCC*), and familial atypical multiple mole melanoma syndrome (p16). Rare kindreds have been identified in whom the 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 (MDCT) or endoscopic ultrasonography (EUS) at regular intervals, but there are no data to support this recommendation. Tumor markers, including K-*ras* and 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 to the liver and lungs but also to 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, and, when present alone, it has been associated with longer survival. An important 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. Approximately 5% to 10% of the population 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 elevated CA19-9 value is reported as low as 50%, missing half of 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 chronic pancreatitis.

Islet amyloid polypeptide, a hormonal factor secreted from pancreatic beta cells, is increased in patients with pancreatic cancer who have glucose intolerance. Currently, it has no proven clinical application.

Imaging Testing for Diagnosis

MDCT with arterial and portal venous phase contrast enhancement ("pancreas protocol CT" [computed tomography]) should be the primary imaging study for the evaluation of patients with symptoms suggestive of pancreatic cancer. It is the appropriate study because it is not only diagnostic but it also can be used to stage the tumor. The increase in sensitivity (about 85%) of dual-phase MDCT 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 MDCT probably is still less than 80%.

Most studies would support a role for EUS in the setting of a small cancer not detected with MDCT. The sensitivity of EUS for identifying a pancreatic mass is reported to be as high as 97%. EUS has been described as the most accurate imaging test for diagnosing pancreatic cancer, being more accurate than transabdominal ultrasonography or CT. However, MDCT with pancreas protocol contrast enhancement has "altered the equation," and currently the role of EUS is in identifying small tumors and in performing fine-needle aspiration (FNA) of the primary tumor or lymph nodes. Although EUS-guided FNA is a safe and effective method to diagnose pancreatic cancer, we rarely perform FNA in patients with evidence of resectable pancreatic cancer because the results do not affect our clinical decision to proceed with surgery. Thus, the role for EUS FNA 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 (Fig. 1 and 2). On contrast-enhanced MDCT images, ductal adenocarcinoma typically appears as an irregular, hypodense lesion. Magnetic resonance imaging (MRI) may be as accurate as MDCT, but generally it is not as readily available and there is not the same expertise in interpreting the findings. EUS may be the most accurate method for staging the local extent (T staging) (Fig. 3) and nodal status (N staging). Correct interpretation of both CT and EUS images regarding resectability varies depending on the study. For EUS, operator experience and the size of the tumor are important variables. Specifically,

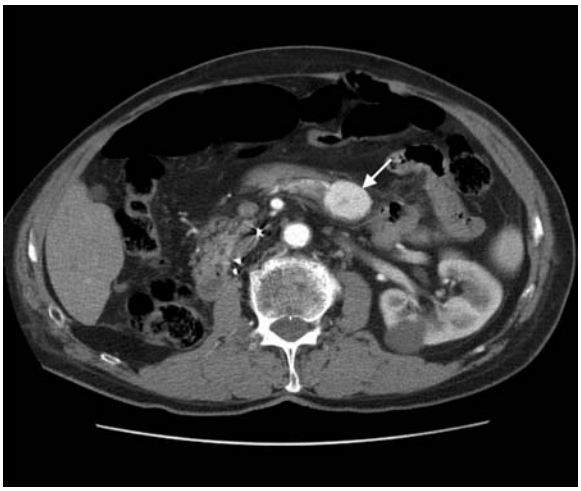

Fig. 1. Computed tomogram showing hyperattenuating lesion in the body of the pancreas (*arrow*). Primary pancreatic adenocarcinoma is usually hypoattenuating. This lesion would also be consistent with an islet cell tumor. The right kidney is absent. This lesion is a metastatic renal cell carcinoma.

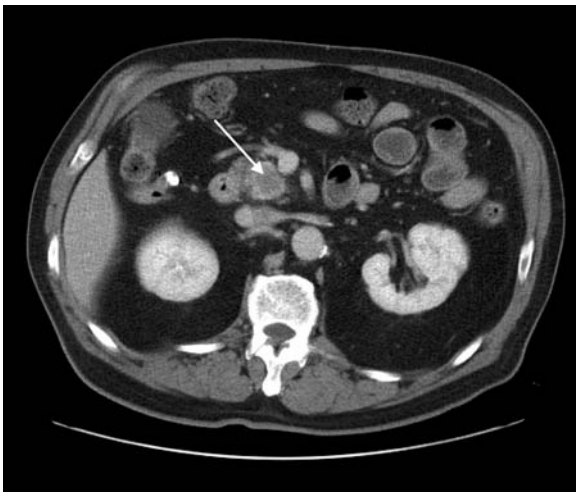

Fig. 2. Computed tomogram showing pancreatic cancer. A small hypoattenuating lesion is seen in the head of the pancreas (*arrow*). The superior mesenteric vessels are not involved by the tumor, which is resectable.

the area of interest relative to 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. Whether advances in EUS technology will improve its ability to determine resectability when CT (or MRI) findings are equivocal is unclear.

Small liver or peritoneal metastases usually are not seen on preoperative imaging studies. Laparoscopy has been recommended by some authors 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, or 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 FNA 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 at surgery. The other 5% usually

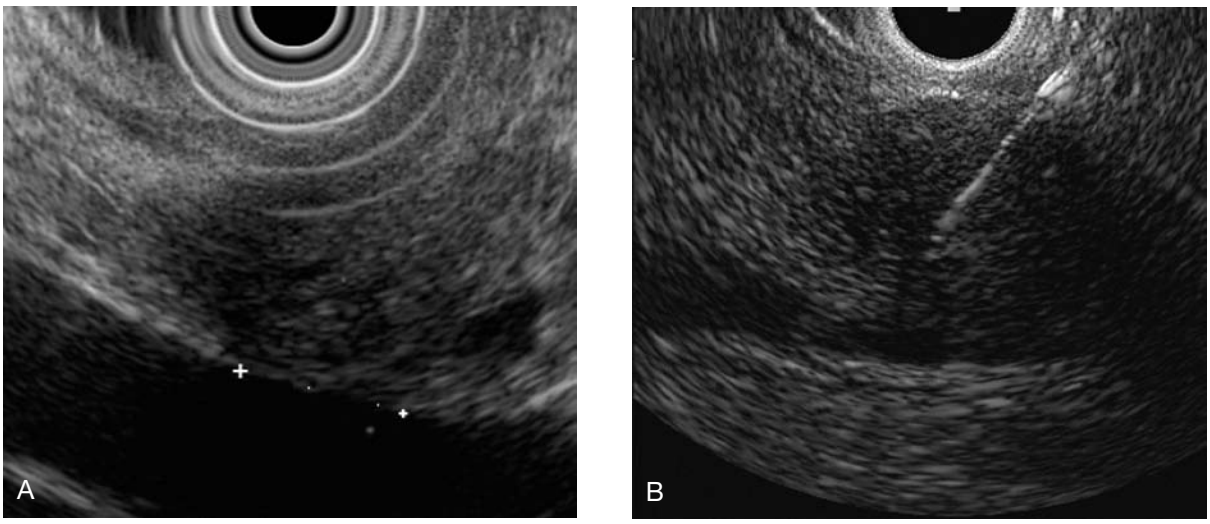

Fig. 3. *A*, Endoscopic ultrasonogram of the pancreatic head shows a poorly defined hypoechoic mass that impinges on the portal vein for a distance of 11 mm (see markers). Surgical resection confirmed invasion of the portal vein. *B*, Fine-needle aspiration of mass shown in *A*.

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 36, "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 FNA.

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 cholecystectomy and removing a portion of the stomach (at least antrectomy), the distal bile duct, head of the pancreas, the duodenum, 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, four prospective, randomized trials have failed to find an advantage for the more extensive procedure.

Surgery is the only chance for cure, but 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 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 our policy—and that of 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. The preferred endoscopic prosthesis for palliation is an expandable metal stent, which is less likely to become occluded than plastic stents. 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 our experience, 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 pancreatic cancer. Chemical intraoperative splanchnicectomy or celiac plexus block performed percutaneously or with EUS reportedly has reduced pain markedly and, according to one report, has prolonged survival. The advantage of plexus block is that it produces fewer complications related to narcotic use, namely, constipation, nausea, and vomiting. Although no controlled trial has tested the efficacy of celiac plexus block

against oral pharmacologic therapy, the current bias is that celiac block provides better pain control.

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 an acetaminophen (325 mg)-oxycodone (5 mg) combination, one or two 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 pain control. A short-acting liquid morphine compound may be useful to control breakthrough pain. Alternatively, a fentanyl (Duragesic) patch, 25 to 100 μg per hour, 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. Our practice has been to prescribe pancreatin (Viokase), 8 tablets with meals (2 tablets after a few bites, 4 during the meal, and 2 at the end of the meal), to correct steatorrhea.

Chemotherapy and Radiotherapy

Chemotherapy

No single or combination chemotherapy is highly effective for pancreatic cancer. Only 5-fluorouracil (5-FU) and gemcitabine have been associated with survival longer than 5 months. 5-FU has been administered as a bolus or short-term continuous infusion or protracted infusion to treat many tumors. However, protracted infusion of 5-FU in combination with other chemotherapeutic agents does not appear to be advantageous. Gemcitabine has a low objective response rate and, compared with 5-FU, a small statistically significant improvement in overall survival (5.7 vs 4.4 months). One-year survival with gemcitabine treatment is 18%, compared with 2% for 5-FU.

Radiotherapy

Radiation is used in two situations. 1) It is used as adjuvant therapy after resection for cure. Until recently, the only randomized trial showed that radiotherapy in combination with 5-FU had a 2-year actuarial survival rate of 43% compared with an 18% rate for the control group (resection only). However, a recently published European study found no significant advantage for radiotherapy. Although this was the largest randomized trial in the postsurgical adjuvant setting (n=541), design flaws of the study led to serious criticism and limited adoption of its conclusion. External beam radiation with 5-FU is the standard of care for adjuvant therapy in most US centers. 2) In unresectable locoregional pancreatic cancer, combined chemoradiation therapy, with 5-FU and radiation, has been shown to be superior to radiation alone, with a median survival of 42 versus 23 weeks.

CYSTIC PANCREATIC TUMORS

Serous Cystadenoma

Classically, the presentation of these tumors is described as large, sometimes palpable, asymptomatic upper abdominal masses, but in our experience, they more frequently are small lesions in the head, body, or tail of the pancreas that are discovered incidentally on imaging studies (Fig. 4). They occur equally in males and females 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 name "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

These tumors 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

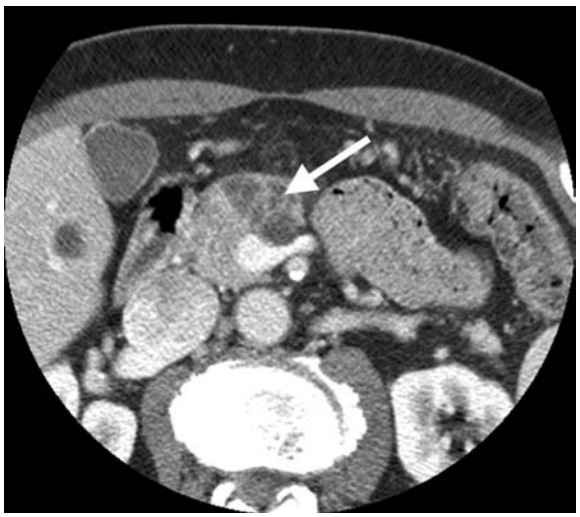

Fig. 4. Computed tomogram showing a serous cyst. The mass lesion in the head of the pancreas consists of multiple small cystic lesions (*arrow*). The findings are typical of serous cystadenoma.

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

This group of tumors, originally described in Japan, consists 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 occurs 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, one-half of 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. When to recommend surgical resection (especially when a Whipple resection is required) is more controversial.

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 one-half of the patients have the diagnostic finding of a patulous papilla extruding mucus. EUS may be helpful in making the diagnosis, and with less risk than ERCP. In addition, EUS can help exclude main-duct involvement and aid the clinician in assessing the risk of malignancy for the patient.

Solid-Cystic (Papillary-Cystic) Tumor

This 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 present. Most patients present with abdominal pain. The treatment for 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. EUS 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 EUS 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. Recently, an international consensus on management was published and recommended careful follow-up with imaging for asymptomatic peripheral cysts 3 cm or smaller.

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CHAPTER 38

Gallstones

Bret T. Petersen, MD

Gallstones are extremely common, occurring in 10% to 20% of women and 5% to 10% of men in Western cultures. They generate an enormous medical and financial burden. More than 500,000 cholecystectomies are performed each year in the United States. Therefore, an understanding of the physiology, presentation, and efficient approaches to management is important. Optimal clinical approaches vary considerably, depending on the presentation.

BILE PHYSIOLOGY

The major components of bile are water, inorganic solutes, and organic solutes. The organic solutes include miscellaneous proteins, bilirubin, bile acids, and the 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 present 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 and chenodeoxycholic acids) are made 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 tenfold for efficient storage during fasting. 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 per day, slowing during fasting and accelerating greatly after meals (Fig. 1).

GALLSTONE PATHOGENESIS AND EPIDEMIOLOGY

Gallbladder stones are made predominantly of cholesterol in 80% of patients and of bilirubin

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography.

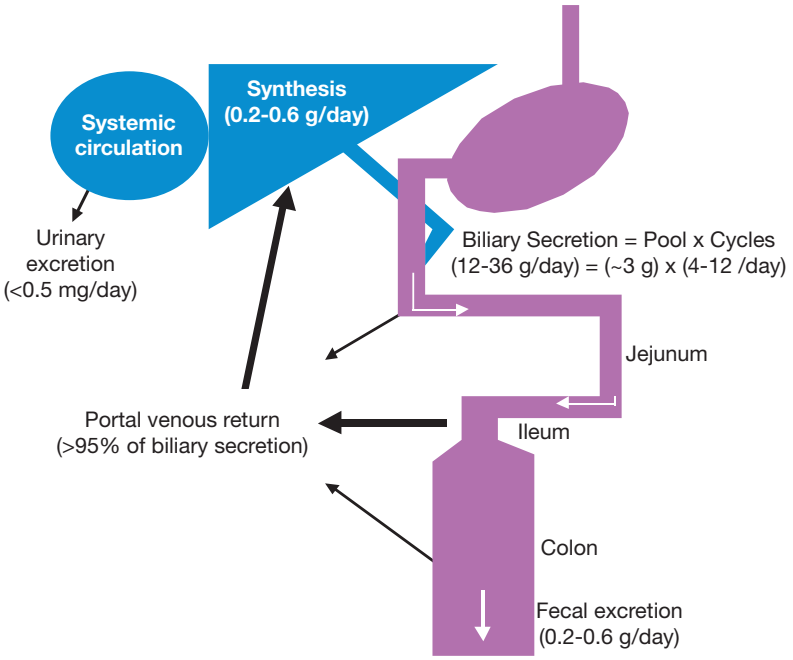


Fig. 1. Enterohepatic circulation. A pool of 3 g of bile acids cycles 4 to 12 times per day. Ileal absorption returns 97% of intraluminal bile acids to the circulation. Ninety percent of bile acids are extracted from the portal system on their first pass through the liver. In health, hepatic synthesis of bile acids is equivalent to enteric losses. (Modified from Zucker SD, Gollan JL. Physiology of the liver. In: Haubrich WS, Schaffner F, Berk JE, editors. Bockus gastroenterology. Vol 3. 5th ed. Philadelphia: WB Saunders Company; 1995. p. 1858-1904. Used with permission.)

pigment in 20% (Fig. 2). Cholesterol stones contain a mixture of 50% to 99% cholesterol by weight, a glycoprotein matrix, and small amounts of calcium and bilirubin. Development of overt stones requires three critical defects related to bile saturation, crystal nucleation, and gallbladder motility.

Cholesterol supersaturation can occur as a result of deficient secretion of bile acid or hypersecretion of cholesterol. Bile acid secretion may be diminished because of reduced synthesis, as occurs with age or liver disease, or because of reduced 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 is increased with hormonal stimuli (female sex, pregnancy, exogenous estrogens, and progestins), obesity, hyperlipidemia, age, chronic liver disease, and sometimes with excessive dietary polyunsaturated fats or calorie intake.

In a supersaturated environment, the initial formation of gallstone crystals occurs as a result of an excess of nucleating versus antinucleating effects of the various proteins in bile.

Gallbladder dysmotility results in inadequate clearance of crystals and nascent stones. Motility is reduced in the presence of supersaturated bile even before stone formation. Reduced 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, are common in most Western populations (15%-20% in women, 5%-10% in men), and occur almost uniformly in North and South American Indians (70%-90% in women). For all populations, the prevalence increases with age and is approximately twice as high in women as in men.

Black and brown pigment stones are a result of increased amounts of unconjugated insoluble bilirubin present in bile, often because of infection or hepatic secretion. Black stones originate in the

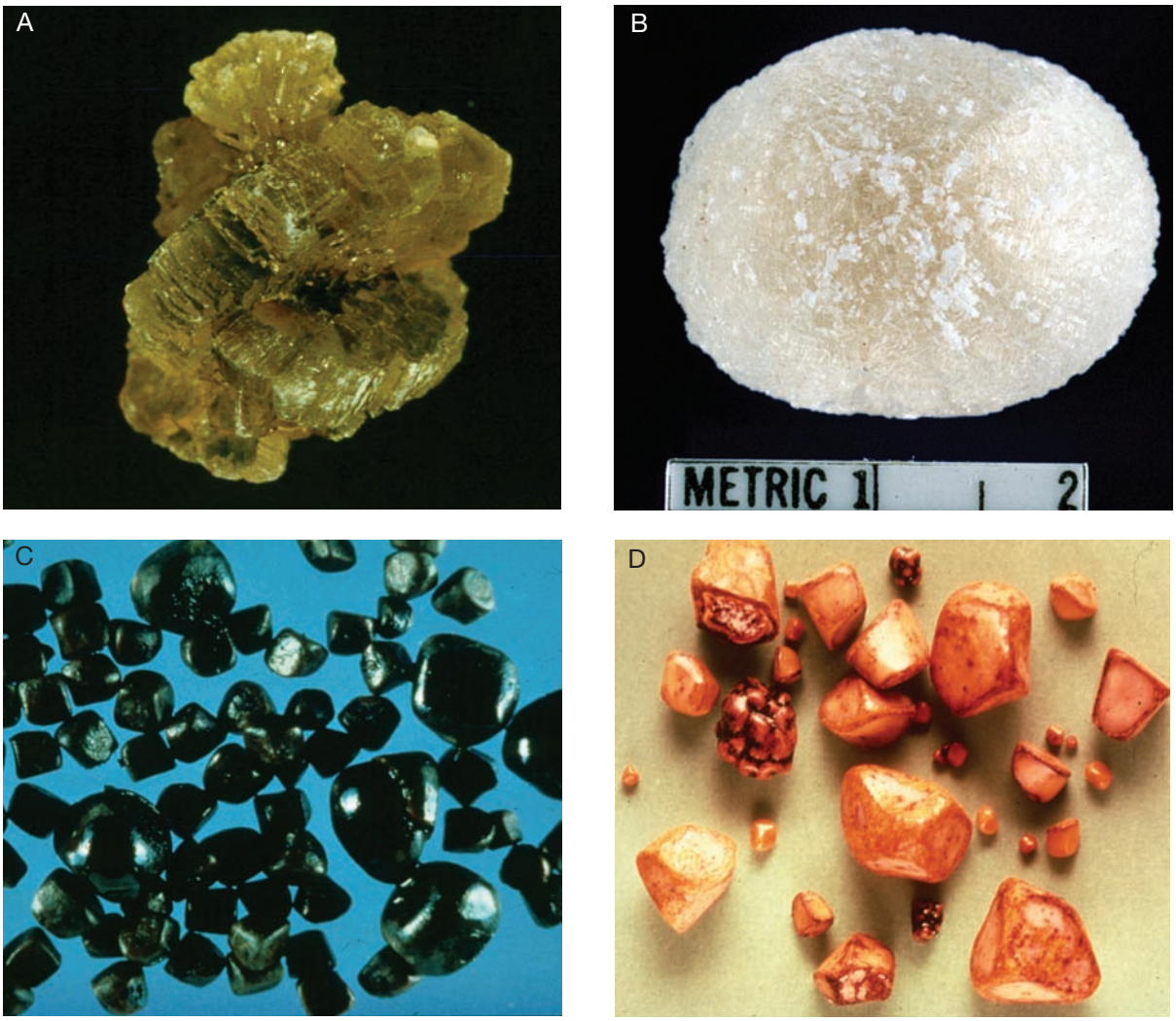


Fig. 2. Variations in morphologic findings of cholesterol gallstones. *A*, Nearly pure 97% cholesterol crystalline stone on a pigmented central nidus. *B*, Pure 99+% cholesterol stone in the conformation of a mothball. *C*, Faceted cholesterol stones with an external shell of black pigment and calcification. *D*, Several morphologic features of mixed, predominantly cholesterol stones from one patient.

gallbladder. They are small, irregular, dense, and insoluble aggregates or polymers of calcium bilirubinate. They may occur with cirrhosis or chronic hemolysis but usually have no identifiable cause (Fig. 3). Brown pigment stones occur primarily in the bile ducts, where they are related to stasis and chronic bacterial colonization—as may occur above strictures or duodenal diverticuli, after sphincterotomy, or in association with biliary parasites. Brown stones are 10% to 30% cholesterol. They are softer than black pigment stones and may soften or disaggregate with cholesterol solvents (Fig. 4).

BILIARY IMAGING

Numerous methods are available for imaging the biliary tree. Some are used primarily to assess the gallbladder or the bile ducts, and others provide a more general assessment of the abdomen, as in patients with undefined pain.

Abdominal Plain Radiography

Abdominal plain radiography detects only 10% to 15% of gallstones, which are calcified sufficiently to appear radiopaque (Fig. 5). Abdominal radiography also may detect aerobilia and porcelain gallbladder.

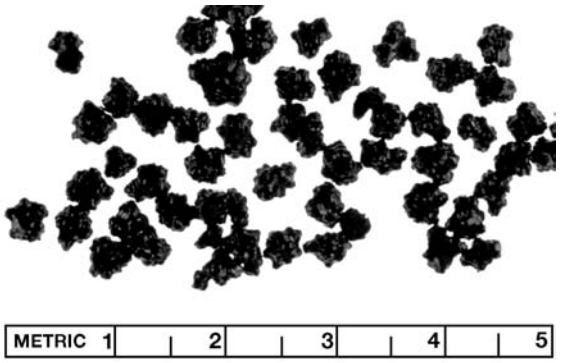


Fig. 3. Black pigment gallstones are formed primarily in the gallbladder and made of dense and insoluble polymers of calcium bilirubinate. They constitute 20% of gallbladder stones. Although associated with increasing age, cirrhosis, and hemolysis, they usually are idiopathic.

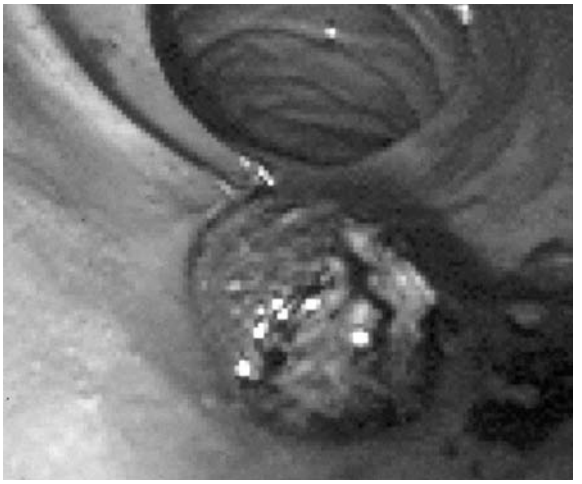


Fig. 4. Brown pigment gallstones are formed in the ducts as primary duct stones. They are composed of calcium bilirubinate and about 30% cholesterol. They are softer and more amorphous than cholesterol or black pigment stones and are associated with strictures, stasis, duodenal diverticuli, and infection. Here, a brown stone is seen in the lumen of the duodenum after extraction, with endoscopic retrograde cholangiopancreatography, from the bile duct.

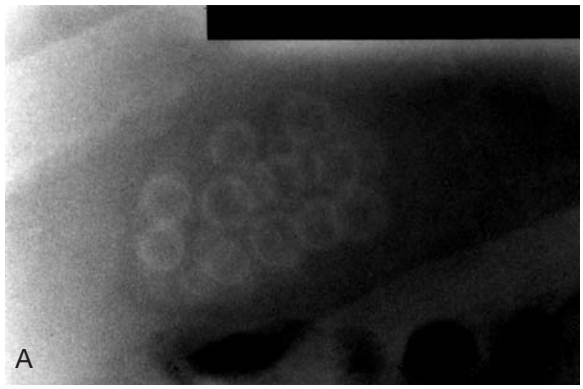
Air within the biliary tree implies the presence of a previous biliary sphincterotomy, a biliary-enteric anastomosis or fistula, or an incompetent sphincter, as may occur with duodenal Crohn's disease, duodenal diverticuli, or other periampullary disease. *Porcelain gallbladder* refers to radiographically detectable deposition of calcium within the gallbladder wall. It has a considerable association with progression to gallbladder cancer and, thus, is an indication for elective prophylactic cholecystectomy.

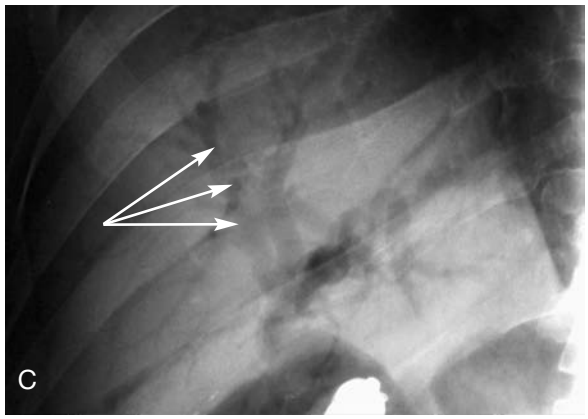
Oral Cholecystography

Oral cholecystography involves standard radiographic imaging of the right upper quadrant after oral administration of a contrast agent (Fig. 6). Normal imaging during oral cholecystography necessitates ingestion, intestinal absorption, liver uptake, biliary excretion, and gallbladder concentration of an iodinated radiodense contrast agent. Sixty to eighty percent of 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 in clinical practice has diminished because it is less sensitive (65%-90%) than ultrasonography for gallbladder stones and it is not indicated when acute cholecystitis is suspected. It may be useful when ultrasonography fails to image the gallbladder or fails to demonstrate stones despite a strong clinical suspicion and for demonstrating cystic duct patency in potential candidates for nonsurgical therapies.

Transabdominal Ultrasonography

Transabdominal ultrasonography is the first choice for evaluation of jaundice and right upper quadrant pain and when cholangitis or cholecystitis is suspected, because it is portable, requires no specific preparation, and uses no radiation (Fig. 7). The examinations are analogous to a physical examination and, hence, are somewhat subjective and operator-dependent. They are compromised by obesity and interfering shadows caused by, for example, ribs, scars, and bowel gas. Ultrasonography is highly sensitive for dilated ducts; however, ducts may be normal in 25% to 35% of patients with choledocholithiasis, particularly when the presentation is acute or associated with biliary fibrosis. The sensitivity of ultrasonography for identification of common duct stones is widely variable (20%-80%). It is most sensitive (90%-98%) for the detection of gallbladder stones that are identified as mobile, intraluminal, echogenic, shadowing particles. Cholecystitis is identified by gallbladder contraction or marked distention with surrounding





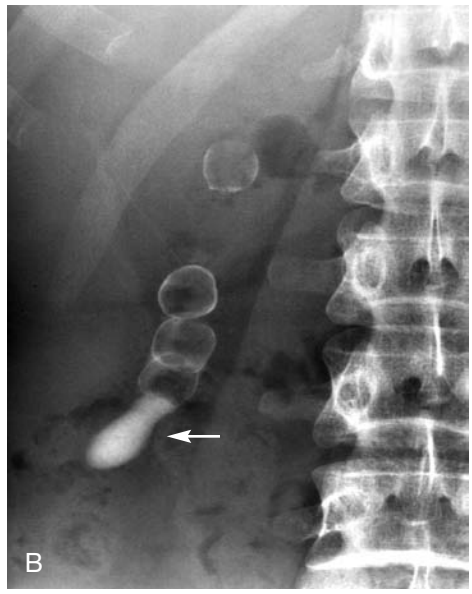


Fig. 5. Abdominal plain radiography. *A*, Radiopaque gallstones; 15% are detected on plain radiography and 50% on computed tomography. No relationship to symptoms. *B*, Radiopaque bile. So-called milk-of-calcium bile (*arrow*) is attributed to chronic gallbladder obstruction and is likely related to symptoms when seen. Here, it is seen below four radiopaque obstructing stones. *C*, Aerobilia (*arrows*), indicative of past sphincterotomy or biliary-enteric anastomosis or fistula. It is sometimes seen with Crohn's disease, diverticula, or other periampullary disease.

fluid or wall thickening. Gallbladder thickening also may be due to portal hypertension, ascites, and hypoalbuminemia.

Endoscopic Ultrasonography

Endoscopic ultrasonography (EUS) is highly sensitive for intraductal stones and slightly less so for gallbladder stones, depending on anatomy. It is an optimal screening tool when the suspicion for bile duct stones is low to moderate, endoscopic examination of the upper gut is also needed, other extraluminal questions exist, or the expense and risk of endoscopic retrograde cholangiopancreatography (ERCP) are unacceptable. Compared with magnetic resonance cholangiopancreatography (MRCP) and ERCP, EUS is the most cost-effective first study for suspected stones when the pretest probability is less than 55% to 60%. ERCP becomes cost-effective above this level, which largely includes only patients with distinctly abnormal liver enzyme values. EUS also can identify gallbladder sludge and microlithiasis in symptomatic patients with negative transabdominal ultrasonographic findings. Patients must be safe candidates for both endoscopy and sedation.

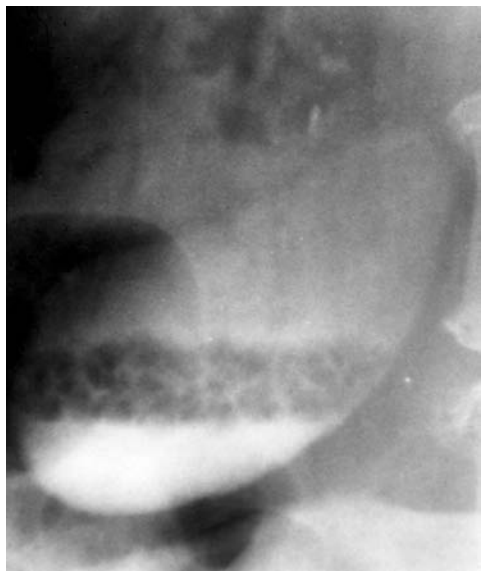


Fig. 6. Oral cholecystography. Floating cholesterol gallstones layering at interface of contrast and bile.

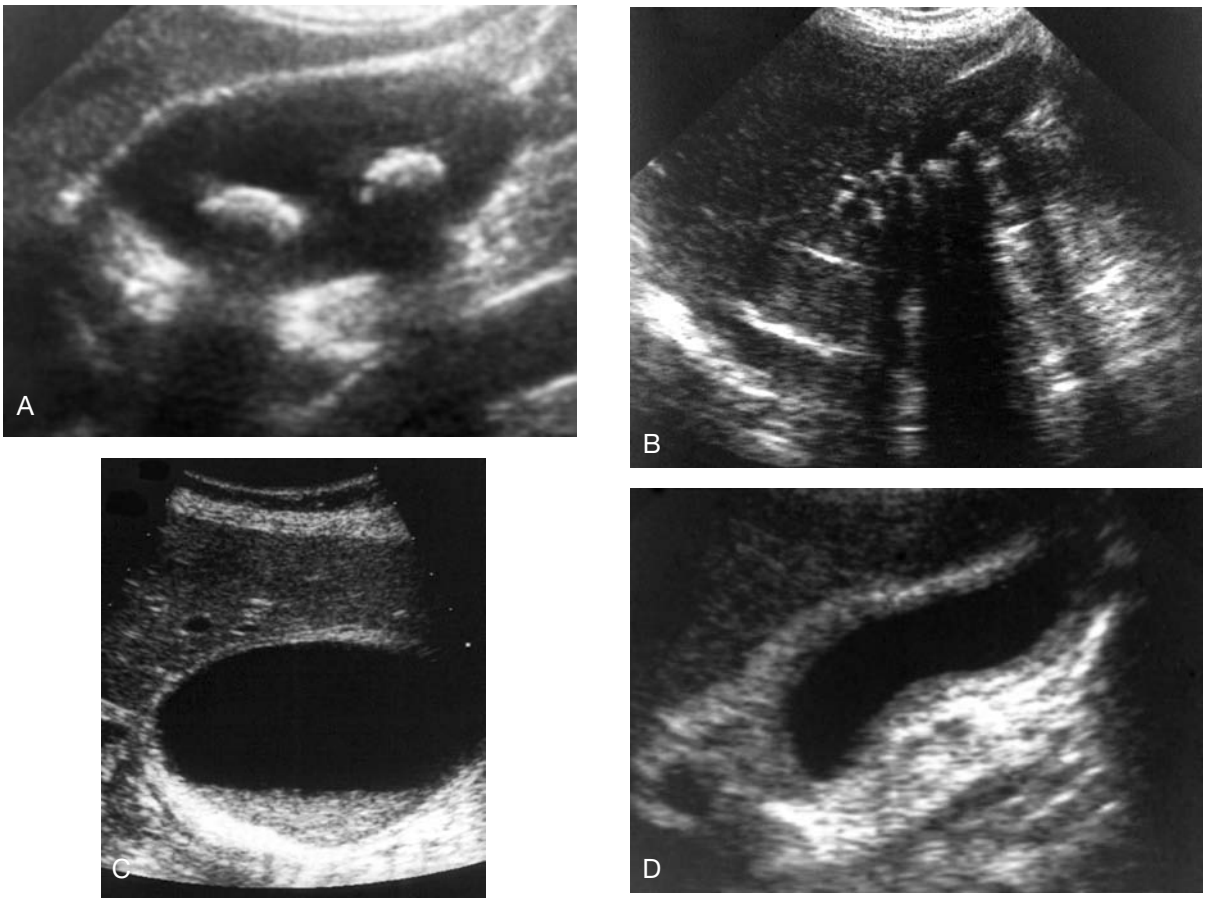


Fig. 7. Gallbladder ultrasonography. *A*, Shadowing, mobile, echodense gallstones in a normal lumen. *B*, Tightly packed and less discrete stones in a contracted gallbladder. *C*, Gallbladder sludge composed of cholesterol crystals and mucus and seen during prolonged gallbladder stasis, as with total parenteral nutrition or during pregnancy. *D*, Thick, edematous gallbladder mucosa sometimes seen with acute cholecystitis, portal hypertension, ascites, or hypoalbuminemia.

Radionuclide Biliary Scanning

Radionuclide biliary scanning, or hepatobiliary iminodiacetic acid scanning, involves noninvasive scanning of gamma emissions after intravenous administration, liver uptake, and biliary excretion of technetium iminodiacetic acid derivatives. Failure to visualize the gallbladder by 4 hours after injection is indicative of obstruction of the cystic duct. The primary clinical indication is for the diagnosis of acute cholecystitis. Nonvisualization of the gallbladder is 97% sensitive and 96% specific for acute calculous cholecystitis. False-negative results occur in acalculous cholecystitis, whereas false-positive results occur in chronic cholecystitis, in chronic liver disease, and during total parenteral nutrition or fasting states. The test is also useful for noninvasive confirmation of intra-abdominal bile leakage.

Abdominal Computed Tomography

Abdominal computed tomography (CT) is the best imaging method for the evaluation of possible complications of biliary stone disease if ultrasonography is compromised or suboptimal, as in patients with fever, right upper quadrant pain, and associated jaundice (Fig. 8). Bowel gas and ribs do not interfere, and CT is better than ultrasonography for obese patients, in whom imaging is improved by discrete fat planes. The test is not appropriate for the diagnosis of uncomplicated stone disease or evaluation of biliary colic, because half of all gallstones are radiolucent on CT.

Cholangiography

Cholangiography can be performed either invasively or noninvasively. The selection of percutaneous transhepatic cholangiography, ERCP, or MRCP is based largely on institutional expertise, therapeutic goals, and the clinical setting.

Endoscopic Retrograde Cholangiopancreatography

ERCP is favored in patients with ascites or coagulation defects, suspected periampullary or pancreatic neoplasia, nondilated ducts, anticipated need for therapeutic maneuvers (stone removal and stenting), hypersensitivity to contrast agents, or failure of percutaneous routes (Fig. 9). Purely diagnostic use is diminishing rapidly because EUS and MRCP serve this purpose more safely in most patients. ERCP is successful in more than 95% of diagnostic applications, 90% to 95% of sphincterotomies and complete stone extraction, and 90% of procedures for stenting of malignant obstruction. The overall risk of the test in patients with suspected gallstones is 2% to 7% for diagnostic procedures and 7% to 10% for therapy. Risks include death, pancreatitis, infection, sedation or cardiovascular events, hemorrhage, and perforation.

Percutaneous Transhepatic Cholangiography

Percutaneous transhepatic cholangiography may be favored in patients with more proximal obstruction (hilar or above), 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 is 3% to 8% and includes death, sepsis, bile leaks, and intraperitoneal bleeding.

Magnetic Resonance Cholangiopancreatography

MRCP is favored in frail patients who are not candidates for conscious sedation and in those with coagulopathy or a need for concurrent staging or evaluation of the liver parenchyma or other organs, especially when there is little likelihood for therapeutic intervention.

GALLSTONE CLINICAL PRESENTATIONS AND MANAGEMENT

Asymptomatic gallstones are a common incidental discovery in the course of various abdominal imaging procedures. Gallstones remain asymptomatic long-term in 70% to 80% of patients. When gallstones eventually become symptomatic, only 2% to 3% of patients present initially with acute cholecystitis or other complications. Asymptomatic stones generally do not require therapy. However, prophylactic cholecystectomy should be considered for patients before extended travel to remote areas (eg, Antarctica) and in American Indian populations, in

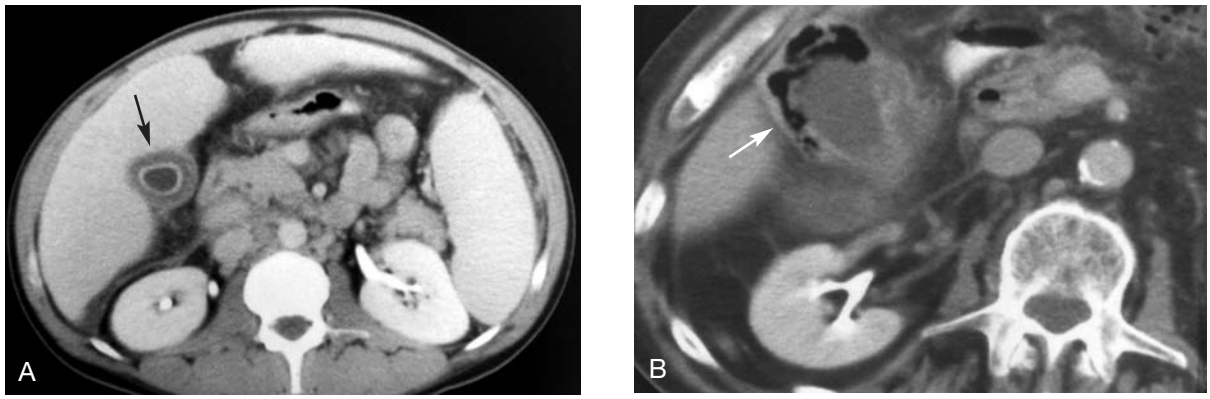


Fig. 8. Computed tomography of complicated biliary stone disease. *A*, Thickened gallbladder wall (*arrow*), as seen in the ultrasonogram in Figure 7 *D*. *B*, Emphysematous cholecystitis (*arrow*) due to *Clostridium* species and others presents with toxicity as a medical and surgical emergency.

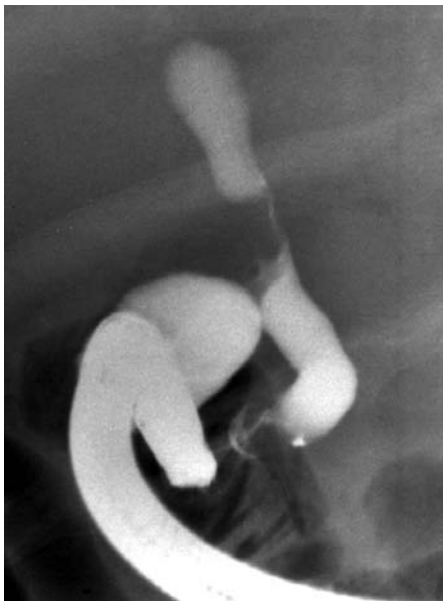


Fig. 9. Endoscopic retrograde cholangiography. Contrast-filled bile duct demonstrates Mirizzi's syndrome, recognized by the unusual eccentric stricture in the mid duct, with nonvisualization of the cystic duct and gallbladder.

whom the relative risk for stone-associated gallbladder carcinoma is 20-fold higher than in those without stones.

Cholecystectomy can be considered during weight loss operations, even without existing stones, because the subsequent development of stones can be anticipated. Cholecystectomy is not recommended for patients with asymptomatic stones who have diabetes mellitus or sickle cell disease if they have usual access to medical care.

Biliary colic is a relatively specific form of pain that usually develops rapidly in the epigastrium or right upper quadrant and lasts longer than 15 minutes but not longer than 4 to 6 hours. A complete history is required to differentiate alternative causes of pain. After symptoms develop, a similar pattern is likely to continue. The likelihood of patients experiencing a severe event or complication is approximately 1% per year, prompting the recommendation for surgical therapy of symptomatic stones. Histologically, most patients with recurrent biliary colic have chronic cholecystitis. Patients with uncomplicated colic require episodic pain management and dietary moderation emphasizing self-selection rather than strict exclusion of fat or other food types. Laparoscopic cholecystectomy is now the standard and most widely used therapy. There is a "learning curve" of at least 10 to 25 procedures, during which time the duration of the procedure and complications are considerably greater. The major risk is for serious duct injuries, which occur in fewer than 1 in 400 cases. Open cholecystectomy is necessary in less than 5% of initial laparoscopic procedures. Conversion itself usually is not considered a complication but an appropriate change in technique based on intraoperative findings. The risk for conversion is higher with acute cholecystitis.

Nonoperative therapy of gallbladder stones is largely of historical interest. A general requirement for all nonsurgical therapies is patency of the cystic duct, as determined with oral cholecystography or radionuclide biliary scanning. Stones that are seen to float above a contrast layer during oral cholecystography are high in cholesterol and very amenable to dissolution (Fig. 6). The major shortcoming of all nonsurgical therapies is the potential for gallstone recurrence, which occurs in 10% to 20% of patients per year and up to 40% to 60% overall for patients with multiple stones. Oral bile acid therapy with ursodeoxycholic acid (7-8 mg/kg per day) dissolves 30% to 80% of radiolucent stones less than 15 mm in diameter over 6 to 24 months. Repeat cholecystography is performed after 6 to 12 months, and therapy is discontinued if no dissolution is evident or if overt rim calcification has developed. Side effects of therapy are infrequent and include diarrhea in 3% to 5% of patients. Extracorporeal shock wave lithotripsy is performed more commonly in Europe than in the United States. One machine has been approved for duct stone applications only, and no machine has been approved in the United States for gallbladder stones. Extracorporeal shock wave lithotripsy is generally safe and well tolerated. Success depends on fragmentation plus either passage or dissolution of the resulting debris. Optimal results are achieved with single radiolucent stones less than 20 mm in diameter, for which clearance is achieved in 70% to 95% after 12 to 24 months of full-dose bile acid therapy. Rapid dissolution of gallstones over 6 to 12 hours can be accomplished by delivery of a cholesterol solvent such as methyl-*tert*-butyl ether into the gallbladder

through a transhepatic catheter. Cholesterol stones that are radiolucent on CT are predictably soluble, independent of their size or number.

Complications of gallstone disease include acute cholecystitis, Mirizzi's syndrome, gallbladder perforation, cholecystoenteric fistulas, "gallstone ileus," and gallstone or biliary pancreatitis.

Acute cholecystitis presents with biliary colic that usually lasts longer than 4 to 6 hours and spreads to involve the parietal surfaces, with evolution from a nonspecific visceral character to a more localized right upper quadrant pain. There may be associated nausea, vomiting, jaundice, fever, and tenderness. The laboratory results are nonspecific and may include leukocytosis and modest increases in aminotransferase, alkaline phosphatase, and amylase levels. Management of acute cholecystitis includes administration of antibiotics, hydration, analgesia, nasogastric suction as needed for comfort, and removal or drainage of the obstructed gallbladder. Gallbladder decompression via percutaneous placement of a cholecystostomy tube is efficacious in patients with substantial operative risk. After days to weeks of antibiotic therapy and passive drainage, subsequent operative or nonoperative management can be pursued electively. Endoscopic drainage also has been described.

Mirizzi's syndrome involves gallbladder obstruction plus obstructive jaundice from stone impaction in the distal cystic duct, with inflammatory compression of the common hepatic duct. The clinical and cholangiographic findings must be differentiated from those of other benign and malignant duct strictures. Treatment is generally surgical, although endoscopic palliation with stenting and stone removal has been described.

Gallbladder perforation from stone-induced inflammation generally is contained locally and rarely is free within the abdomen. Perforation with abscess formation occurs especially with minimally symptomatic smoldering disease in elderly patients.

Cholecystoenteric fistulas can develop as a result of gallbladder perforation and decompression into any neighboring viscus. They usually involve the duodenum or the hepatic flexure of the colon. When fistulas develop to the colon, patients may present with new onset of watery bile acid diarrhea or cholangitis from colonic contamination of a diseased gallbladder.

Gallstone ileus results after the passage of a stone through a fistula and subsequent obstruction in a narrow downstream section of gut. This is most common in the terminal ileum. Gallstone ileus occurs especially in elderly women. The clinical presentation is that of intestinal obstruction with aerobilia seen on plain radiography or CT. Management is surgical.

Gallstone or biliary pancreatitis manifests acutely as a result of temporary stone impaction or traversal through the sphincter of Oddi. The best indicator of a biliary cause is an acute increase in aminotransferase values (more than threefold) at initial presentation. Corroborating findings include a dilated bile duct and stones within the gallbladder.

CHOLEDOCHOLITHIASIS

Most bile duct stones originate in the gallbladder, and 5% to 15% of patients undergoing cholecystectomy have concurrent duct stones. Coexistent duct and gallbladder stones generally have the same composition: 70% are cholesterol stones and 30% are pigment stones. Primary duct stones are brown pigment stones, which differ from the smaller, harder, black pigment stones found in the gallbladder.

The presentation of duct stones varies and ranges from few or no symptoms to overt cholangitis or pancreatitis. The development of secondary biliary cirrhosis related to ductal pressure rarely occurs in the absence of clinical symptoms or laboratory abnormalities. Classically, stone-related obstruction is recurrent and incomplete. Increases in bilirubin and alkaline phosphatase levels are less marked than those for fixed malignant obstruction; the bilirubin level usually peaks at 12 to 14 mg/dL. Ninety percent of obstructing duct stones are located distally near the ampulla, where visualization with ultrasonography and CT is difficult. Definitive identification requires cholangiography. Once identified, duct stones should be removed, usually through ERCP with sphincterotomy. Extracorporeal shock wave lithotripsy of duct stones is clinically approved and feasible. It usually is coupled with ERCP removal of stone debris. Stones identified at operation can be removed through percutaneous T-tube tracts 4 to 6 weeks postoperatively. This is successful in 96% of

patients, and the morbidity rate is 4%. No primary dissolution therapy is available for common duct stones, although reports of softening or disaggregation of brown pigment stones occasionally prompts use of ursodeoxycholic acid before ERCP is repeated.

Optimal management for healthy patients with concurrent gallbladder and bile duct stones is incompletely defined. Currently, the usual practice combines therapeutic ERCP with laparoscopic cholecystectomy. Laparoscopic duct exploration is still not widespread, although data suggest it is associated with lower morbidity and incurs lower costs than postoperative ERCP.

Elective management of gallbladder stones after resolution of cholangitis and endoscopic clearance of duct stones is somewhat controversial. For high-risk patients, clearance of duct stones alone often is adequate. Experience suggests relative safety for observation alone. Biliary colic or cholecystitis that requires therapy subsequently develops in 15% to 20% of patients. This risk justifies prophylactic elective cholecystectomy in average-risk patients.

CHOLANGITIS

Acute bacterial cholangitis is due to infection in obstructed bile ducts. It is caused most commonly by obstructing stones and occurs only infrequently with benign or malignant strictures. Charcot's triad (fever and chills, jaundice, and abdominal pain) is present in perhaps 60% of cases. Diagnosis may be difficult in elderly patients, who may not have jaundice or pain. Acute cholangitis is a medical emergency when fever exceeds 40°C or is associated with sepsis, hypotension, peritoneal signs, or a bilirubin concentration more than 10 mg/dL. CT or ultrasonography is supportive of the diagnosis. Most episodes are due to coliforms such as *Escherichia coli*, *Klebsiella* (70% of episodes), *Enterococcus*, and anaerobes (10%-15%). Initial therapy includes empiric use of antibiotics, including broad-spectrum agents such as ampicillin plus an aminoglycoside, extended-spectrum penicillins, or third-generation cephalosporins, with or without the addition of specific anaerobic coverage. From 85% to 90% of patients have a response to initial antibiotic and supportive therapy before biliary intervention. Biliary drainage is mandatory, however. Its urgency depends on the initial response to antibiotics and supportive care. ERCP with nasobiliary drain placement, stent, or sphincterotomy and duct clearance is associated with considerably lower morbidity and mortality than traditional surgical management. If endoscopy fails to achieve access, subsequent percutaneous or surgical decompression should be pursued, depending on the clinical urgency.

Patients with *recurrent pyogenic cholangitis*, or oriental cholangiohepatitis, present with recurrent, progressively severe, and frequent attacks of cholangitis with associated extensive stone disease, especially of the intrahepatic ducts. Secondary duct dilation, 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* or *Clonorchis*), and chronic intrahepatic bacterial colonization from unclear sources. Therapy is directed toward 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.

BILIARY STRICTURES

Iatrogenic bile duct strictures develop after 1 in 200 to 1 in 1,000 cholecystectomies. Presentation may be months to years after the injury. When duct injury is recognized intraoperatively, the ideal management is primary surgical repair with choledochojejunostomy. When treated at first presentation with a surgical Roux-en-Y hepaticojejunostomy, 85% to 90% of patients have good long-term results. Endoscopic therapy is now common, however, and 75% to 85% of patients have good results 5 to 10 years later. Recent series have reported better results with maximal caliber dilation and stenting for 6 to 12 months. Anastomotic bile duct strictures are treated much like other iatrogenic lesions, with endoscopic dilation and stenting when accessible.

Inflammatory bile duct strictures occur with primary sclerosing cholangitis and acute or chronic pancreatitis. Those related to chronic fibrotic pancreatitis are best treated surgically with a biliary enteric anastomosis. Strictures from acute pancreatitis usually can be palliated with endoscopic stenting until the acute inflammatory phase resolves. The optimal management of primary sclerosing cholangitis-related dominant strictures is debated, but it generally involves endoscopic balloon dilation with or without stent placement rather than operation. Intervention is used only for stricture or stone-related clinical decline, such as cholangitis, pain, or jaundice.

Currently, most benign strictures of the extrahepatic ducts are treated, at least initially, with endoscopic balloon dilation and stenting. Indications for endoscopic or percutaneous treatment of biliary strictures, in preference to surgery, include recurrence after operative repair, poor operative risk, portal hypertension, high stricture with little or no proximal extrahepatic duct (type 3 or 4), absence of proximal dilation, dominant stricture of primary sclerosing cholangitis (potential liver transplantation), and short-term palliation of acute or chronic pancreatitis-induced stricture.

ELUSIVE BILIARY-TYPE PAIN SYNDROMES

When patients present with recurrent right upper quadrant pain, often subsequent to cholecystectomy, several potential causes must be considered.

Nonbiliary sources of pain, such as functional or irritable bowel syndrome, nonulcer dyspepsia, gastroesophageal reflux, pancreatic disease, or even cardiac disease, may present with features suggesting a biliary source. When treated with cholecystectomy, they typically recur. Diagnosis is largely through careful history and selective use of diagnostic testing.

Gallbladder dyskinesia, sometimes termed *cystic duct syndrome* in the surgical literature, refers to a poorly contractile gallbladder as demonstrated with cholecystokinin-stimulated radionuclide biliary scanning or ultrasonographic volumetric studies. The pathogenesis of pain is not known, but it may be related to a diseased gallbladder wall or a small duct relative to gallbladder size. Data suggest that cholecystectomy affords pain relief to patients with markedly diminished stimulated ejection fractions. Reproducibility of testing has been demonstrated only for gallbladder contractions with the use of weight-based infusions of cholecytokinin rather than bolus injections or alternative means of stimulation.

Microlithiasis refers to the presence and symptomatic passage of small crystalline aggregates or stones that go undetected on ultrasonography. A patient's stone-forming disposition can be inferred from the identification of cholesterol crystals or calcium bilirubinate aggregates during polarized microscopy of a centrifuged bile pellet (Fig. 10). Positive microscopy findings are considered an indication for cholecystectomy, or for sphincterotomy if the gallbladder has already been removed; however, microlithiasis is uncommon in this setting. Sludge or microlithiasis may be demonstrable also with EUS when transabdominal imaging results are normal.

Sphincter-of-Oddi dysfunction refers to a continuum of stenosing or hypertonic abnormalities of the biliary or pancreatic sphincter. It is presumptively diagnosed on the basis of specific symptoms and laboratory criteria. *Type I* is sometimes referred to as *papillary stenosis*. Features include pain, dilated ducts, pain-associated aminotransferase abnormalities, and delayed drainage during cholangiography. It can be treated with sphincterotomy without previous confirmatory tests. *Type II* features pain and one or two of the associated features of type I. Type II is commonly confirmed manometrically before therapy by the demonstration of intercontractile resting sphincter pressures of more than 40 mm Hg. Semiempirical sphincterotomy probably can be justified for patients with classic recurrent short-lasting increases in aminotransferase levels during pain. Presumptive *type III* is associated with pain alone and none of the more objective supporting features. Type III should not be investigated with manometry before a thorough search is made for alternative causes of pain and trials of medical therapies directed toward functional syndromes are completed. ERCP should not be performed to exclude stones or other abnormalities without the availability of manometry. Hence, EUS or MRCP may be preferable early investigations in most

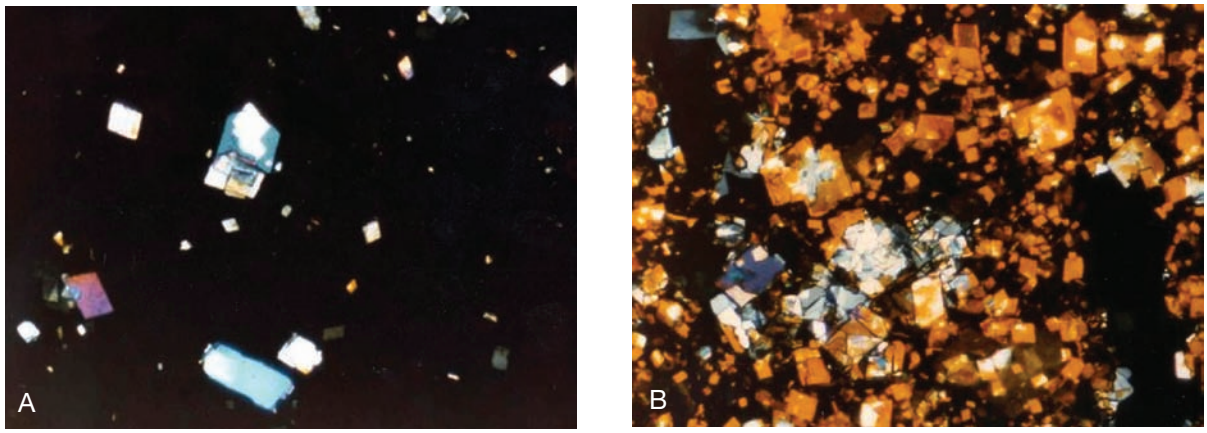


Fig. 10. Polarized microscopy of bile. *A* and *B*, Microscopic examination of sediment after centrifugation of bile shows birefringent rectangular notched crystals. Their identification confirms stone-forming physiology and the potential for an association between gallstones and the patient's symptoms. In *B*, the amorphous golden material is aggregated bilirubinate salts, which may occur with cholesterol crystals or alone. They also indicate a stone-forming propensity.

patients. It should not be treated with sphincterotomy in the absence of abnormal manometry results. Manometry results are abnormal in 15% to 60% of patients, depending on selectivity of testing, and response to sphincterotomy is about 70% in patients with abnormal pressures.

BILIARY LOOK-ALIKES

Intravenous ceftriaxone may lead to the 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 presents as a syndrome of pain, fever, and cholestatic hepatitis, which mimics acute cholecystitis. It is important to elicit an antibiotic history during an evaluation of symptoms. A consistent history and associated eosinophilia may assist in identifying the syndrome.

Leptospirosis has a severe form termed *Weil's syndrome*, which is characterized by fever, jaundice, azotemia, and right upper quadrant pain. The presentation may mimic that of acute bacterial cholangitis. Clues to the diagnosis include a history of exposure risk, myalgias, ocular pain, photophobia, azotemia, and abnormal urinalysis findings.

Pancreas and Biliary Tree

Questions and Answers

QUESTIONS

Abbreviations used:
ALT, alanine aminotransferase
AST, aspartate aminotransferase
CT, computed tomography
ERCP, endoscopic retrograde cholangiopancreatography
EUS, endoscopic ultrasonography
MEN, multiple endocrine neoplasia
MRI, magnetic resonance imaging
TPN, total parenteral nutrition

Multiple Choice (choose the best answer)

1. A 29-year-old man is referred for recurrent episodes of pancreatitis. His first episode of pancreatitis occurred at age 10 years. His attacks occur once a year and lead to hospitalization for a week. In between episodes, he does not experience any discomfort. So far, he has not had any complications. On further questioning, he states that his father and paternal aunt have also had pancreatitis and have undergone pancreatic surgery. He has smoked a pack of cigarettes a day for the past 10 years, but only occasionally consumes alcohol. ERCP at an outside institution showed a 6-mm pancreatic duct without strictures, with multiple dilated side branches. The most likely cause of pancreatitis in this patient is:

a. Cationic trypsinogen gene mutation
b. Heterozygous *SPINK1* gene mutation
c. Heterozygous *CFTR* gene mutation
d. Von Hippel-Lindau gene mutation
e. Gallstone pancreatitis

2. A 40-year-old man who has been drinking approximately 5 cans of beer/day for the past 15 years is admitted with complaints of nausea, vomiting, and abdominal pain. On examination, he is afebrile and in no acute distress. Abdominal examination shows tenderness in the upper abdomen. Laboratory findings include amylase >10 times the upper limit of normal. This is his fourth bout of pancreatitis in 5 years. Which of the following would *not* strongly suggest the diagnosis of chronic pancreatitis?

a. A dilated pancreatic duct with glandular atrophy
b. Scattered calcification in the body and tail of the pancreas
c. EUS performed 3 months after the attack showing lobularity of the parenchyma and hyperechoic foci (2 of 9 criteria)
d. Fecal fat estimation on a 100-g fat diet showing 40 g of fat per day
e. Pancreatic exocrine glandular fibrosis and atrophy found on surgical biopsy

3. A 45-year-old woman who had gastric bypass surgery 6 months ago presents with complaints of greasy, oily stools associated with a 20-lb weight loss. She has a voracious appetite but

hesitates to eat because it worsens her diarrhea. She has no history of pain or pancreatitis. She has never consumed alcohol or smoked tobacco. Her family history is noncontributory. A 72-hour stool fat collection on a 100-g fat diet showed 70 g of fat per day. Serum calcium and triglyceride levels were normal. Which of the following does *not* result in inadequate production or action of pancreatic enzymes?

a. Severe villous atrophy associated with celiac sprue
b. Autoimmune pancreatitis
c. Roux-en-Y gastric bypass surgery
d. Zollinger-Ellison syndrome
e. α_1-Antitrypsin deficiency

4. A 23-year-old female college student presents with severe, constant abdominal pain, nausea, and vomiting which began 3 days ago. She previously has been well. During the last 8 years, her alcohol consumption has steadily increased to "several drinks a day." The serum level of amylase is increased more than 7 times normal. Liver function tests are normal. The serum triglyceride level is inceased at 620 mg/dL. Which of the following statements is most correct?

a. A serum lipase level is needed to confirm the diagnosis of acute pancreatitis
b. Amylase levels more than fivefold normal predict severe pancreatitis
c. The increased serum triglyceride level suggests pancreatitis due to hyperlipidemia
d. Three days from the onset of symptoms, the serum lipase level is more likely to be increased than the serum amylase level
e. Ultrasonography of the gallbladder that shows no stone excludes biliary pancreatitis

5. A 46-year-old woman presents with severe, constant upper abdominal pain, fever, vomiting, and new jaundice. She drinks one or two alcoholic beverages a week and never has been hospitalized except for the deliveries of her five children. Her serum amylase and lipase levels are increased more than 5 times normal. ALT is 412 U/L. She has been receiving broad-spectrum antibiotics since admission, but she continues to have pain, fever, and vomiting. Which of the following is the best course of action?

a. Urgent ERCP if ultrasonography shows a common bile duct stone
b. Urgent ERCP if ultrasonography shows a dilated bile duct
c. Urgent ERCP if a nuclear medicine scan does not show excretion of contrast into the duodenum
d. Urgent ERCP if altered mental status develops
e. Urgent ERCP

6. A 65-year-old man is admitted to the intensive care unit with severe acute pancreatitis. Which of the following is most predictive of severity?

a. His age
b. Gallstone pancreatitis as a cause
c. Persistent organ failure
d. Pulmonary infiltrates
e. C-reactive protein level greater than 150 mg/dL at 48 hours

7. A 65-year-old man is admitted to the hospital with severe acute necrotizing pancreatitis. After a few days, he is still unable to take adequate calories by mouth and still has some abdominal pain. Which of the following is most likely to help him?

a. Enteral feeding by nasogastric tube
b. TPN
c. Somatostatin
d. Broad-spectrum antibiotics
e. Enteral feeding by nasoduodenal tube placed well beyond the pylorus

8. A 68-year-old man has a 3-month history of mild dyspeptic symptoms and a 15-lb weight loss. Findings on upper endoscopy were normal. Six weeks of proton pump inhibitor therapy has not produced any improvement. For 3 days, he has had dark urine and pale stool. He was

brought to the emergency department by his family when they noted scleral icterus. On physical examination, he is comfortable and afebrile with normal vital signs. He is visibly jaundiced, but the examination findings are otherwise normal. Biochemical studies show a bilirubin level of 10 mg/dL (direct, 6 mg/dL) and a threefold increase in the aminotransferase and alkaline phosphatase levels. Bedside ultrasonography shows gallstones and a dilated biliary tree. Which of the following is the best option?

a. Immediate admission to the hospital for observation and blood cultures
b. Urgent ERCP and bile duct decompression
c. Viral serologic testing, stop proton pump inhibitor therapy, and refer to a hepatologist
d. Contrast-enhanced CT of the abdomen
e. Referral to a surgeon for cholecystectomy

9. Which of the following is most correct about neuroendocrine tumors of the pancreas?

a. Nearly all the tumors are associated with MEN 1 syndrome
b. Other features of MEN 1 syndrome include pheochromocytoma
c. The most common peptide expressed is pancreatic polypeptide that causes a watery diarrhea
d. Nonfunctioning islet cell tumors account for at least 50% of the tumors
e. Neuroendocrine tumors associated with MEN 1 tend to be solitary and are rarely malignant

10. A 45-year-old gravida 5 para 5 woman in otherwise good health has three discrete episodes of epigastric abdominal pain lasting 1 to 3 hours. Abdominal ultrasonography shows three gallstones in the gallbladder. Which physiologic alteration most likely is *not* responsible for the gallstones in this patient?

a. Deficient secretion of bile acid
b. Cholesterol supersaturation
c. Imbalance of nucleating and antinucleating factors
d. Relative gallbladder dysmotility
e. Excess bilirubin secretion

11. A 30-year-old African American man with sickle trait develops severe right upper quadrant pain with vomiting. His pain lasts approximately 4 hours. A plain film of the abdomen shows calcified densities in the gallbladder. Which of the following statements about these densities is most likely correct?

a. They are brown pigmented stones
b. If surgery is not feasible, the patient would benefit from treatment with ursodeoxycholic acid
c. They are black pigment stones, which are composed of calcium bilirubinate and account for 80% of common duct stones
d. Cirrhosis is a risk factor for these stones that contain less than 50% of cholesterol
e. Duodenal diverticula predispose to the formation of these stones

12. A 45-year-old woman has abdominal ultrasonography for postprandial diarrhea and lower abdominal cramping relieved by defecation. Several 8-mm mobile stones are found in a nondilated gallbladder. The bile ducts and liver function tests are normal. Which of the following is most likely?

a. As she ages, the likelihood of symptomatic biliary colic developing is 50%
b. Complications occur at a rate of 10% per year
c. Diabetes mellitus in the patient would warrant cholecystectomy
d. Her lifetime risk of symptoms is 20%
e. It is likely that her first presentation will be pancreatitis

13. A 45-year-old woman undergoes laparoscopic cholecystectomy for classic biliary colic with multiple gallbladder stones and a normal-caliber bile duct. Two days postoperatively, she has recurrent pain, a tender abdomen, bilirubin 1.9 mg/dL, and normal AST, ALT, and alkaline phosphatase levels. CT shows a new intra-abdominal fluid collection, and

ERCP is "normal." Which of the following is the most likely cause of this patient's postoperative problem?

a. Leaking hepatic segment with anomalous biliary drainage
b. Acute pancreatitis with pseudocyst formation
c. A retained and now passed common bile duct stone
d. Dropped intraperitoneal gallstone
e. Missed common bile duct stone

14. A 25-year-old woman presents with a 2-year history of daily upper abdominal pain. Most of the symptoms occur postprandially. She rarely vomits and has had no weight loss. Physical examination findings are normal. An extensive series of studies, including endoscopy and abdominal imaging with ultrasonography and CT, have been negative. Laboratory studies repeated 3 times during pain are normal except for a 1.5- to 2.0-fold increase in the amylase level with normal lipase level. Which of the following is most likely?

a. This is a disease that accounts for 10% of unexplained chronic abdominal pain
b. The clearance of amylase in the urine would be low
c. A threefold increase in the serum amylase level would exclude this condition
d. ERCP would be indicated to diagnose early chronic pancreatitis
e. The diagnosis of chronic pancreatitis is secure

15. A 29-year-old man presents with recurrent episodes of pancreatitis that began at age 10 years, and occur approximately once a year. He has no symptoms otherwise. His father and paternal aunt had pancreatitis that required surgery. He rarely drinks alcohol but smokes a pack of cigarettes daily. CT of the pancreas shows diffuse calcifications, and ERCP shows an 8-mm pancreatic duct with multiple dilated side branches. Which of the following would be most appropriate?

a. Referral to a surgeon for Puestow procedure
b. Genetic counseling and testing for cystic fibrosis gene mutations
c. ERCP with sphincterotomy and pancreatic duct stone clearance
d. Yearly endoscopic ultrasonography and CA19-9 testing for cancer screening
e. Genetic counseling and testing for cationic trypsinogen gene mutations

ANSWERS

1. Answer a

The history of early onset of pancreatitis and strong family history of pancreatitis are highly suggestive of hereditary chronic pancreatitis. Mutations in the cationic trypsinogen gene (R117H and N21I) are the most common gene mutations associated with an autosomal dominant pattern of inheritance of pancreatitis. Mutations in *SPINK1* and *CFTR* genes are associated with idiopathic pancreatitis. Von Hippel-Lindau gene mutations are not associated with pancreatitis; these patients may have serous cystadenomas of the pancreas. Gallstone pancreatitis does not cause chronic diffuse pancreatic ductal abnormality.

2. Answer c

Chronic pancreatitis is a histologic diagnosis. However, this "gold standard" is rarely available. Thus, surrogate clinical markers are used to diagnose chronic pancreatitis. In a patient with recurrent pancreatitis, all of the following would strongly suggest the diagnosis of chronic pancreatitis:

1. Histologic study shows features typical of usual chronic pancreatitis
2. Pancreatogram shows marked abnormalities (Cambridge II or III)
3. Calculi in the pancreatic duct are seen on plain radiographs of the abdomen, CT, MRI, or EUS
4. EUS shows ≥5 criteria (<5 criteria are nonspecific and cannot be used to diagnose chronic pancreatitis)
5. Pancreatic function is markedly depressed (pancreatic steatorrhea)

3. Answer e
Depressed pancreatic function occurs in severe celiac sprue. This is thought to result from lack of release of cholecystokinin from a severely affected duodenal mucosa. Pancreatic function recovers with recovery of intestinal villous architecture. Autoimmune pancreatitis is a fibroinflammatory disorder that can cause marked pancreatic atrophy and, consequently, pancreatic insufficiency. Gastric bypass surgery is intended to cause poor mixing of food and pancreatic enzymes and bile. The common channel where food and pancreaticobiliary secretions mix is generally about 100 to 150 cm from the ileocecal valve. The large amount of acid secreted in Zollinger-Ellison syndrome inactivates pancreatic enzymes. However, a large volume of gastric and pancreatic secretions and mucosal injury due to acid overproduction also contribute to diarrhea in Zollinger-Ellison syndrome. α_1-Antitrypsin deficiency is not known to affect pancreatic function.

4. Answer d
The diagnosis of pancreatitis does not need to be confirmed with a serum lipase level because the presentation is typical and serum amylase level is increased at least 2- to 3-fold normal. The degree of increase in the amylase or lipase level does not predict the severity of acute pancreatitis. Her triglyceride level is not even in the range (>1,000 mg/dL) that would be suspicious for pancreatitis due to hyperlipidemia, and it would be necessary to check it again after the acute pancreatitis resolves, because a modest increase due to pancreatitis from other causes often improves or normalizes with resolution of the acute episode of pancreatitis. Normal gallbladder findings on ultrasonography never exclude biliary pancreatitis. With acute pancreatitis, the serum lipase level remains elevated longer than does the serum amylase level.

5. Answer e
With the lack of significant alcohol history, multiple pregnancies (risk for gallstones), and increased ALT level, this patient most likely has acute biliary pancreatitis. Because of persistent fever, pain, and vomiting as well as jaundice, despite antibiotic therapy, she needs urgent ERCP for cholangitis, even if ultrasonography does not show ductal dilation or a stone in the common bile duct. Because of the acute pancreatitis and jaundice, a nuclear medicine scan is unlikely to be helpful. Waiting for further deterioration (altered mental status) in the condition of this patient, who has cholangitis, before performing ERCP is not justified.

6. Answer c
The cause of acute pancreatitis is not clearly a predictor of severity. Age older than 60 years, a body mass index greater than or equal to 30, very increased level of C-reactive protein, pleural effusion, and pulmonary infiltrates are all predictors of severity. Persistent organ failure as well as multiple organ failure is among the strongest predictors of severity.

7. Answer e
At this early stage, and in the absence of documented infection, it is unlikely that antibiotic therapy will be helpful. Somatostatin has not been shown to be helpful in this setting. Nasogastric tube feeding, similar to oral feeding, is not likely to be tolerated. Nasojejunal, or (more often in practice) nasoduodenal, feeding is preferred to TPN because it is cheaper, helps preserve the gut mucosal barrier, and hence reduces the rate of infection, which is higher with TPN.

8. Answer d
This patient has painless jaundice and does not need urgent ERCP or blood cultures in the absence of cholangitis. Because the dilated ducts and clinical presentation do not support an intrahepatic cause, viral serologic testing is not likely to be helpful. Although ultrasonography shows gallbladder gallstones, the lack of pain argues against choledocholithiasis as a cause of the jaundice; hence, cholecystectomy is not necessary. CT is likely to show a mass lesion in the head of the pancreas that would account for this presentation, most likely pancreatic adenocarcinoma.

9. Answer d
Most neuroendocrine tumors of the pancreas are *not* associated with MEN 1 syndrome, which does not include pheochromocytoma. Many neuroendocrine tumors produce pancreatic polypeptide, but this hormone does not cause watery diarrhea. At least half of all islet cell tumors are nonfunctioning.

With MEN 1 syndrome, neuroendocrine tumors are more often multifocal and invasive.

10. Answer e
This multiparous woman most likely has cholesterol-rich gallstones and not black (bilirubin) or brown (pigment) stones. She is unlikely to have excessive hepatic secretion of bilirubin. She very well could have some combination of the following: deficient secretion of bile acid, cholesterol supersaturation, gallbladder dysmotility, and an imbalance of nucleating and antinucleating factors in the bile.

11. Answer d
These calcified densities in the right upper quadrant likely represent gallstones. In this patient, they are black pigment stones, which are related to hemolysis as well as to cirrhosis; they form primarily in the gallbladder. Brown pigment stones, which calcify, usually form in the bile ducts and are related to stasis (duodenal diverticula) and infection. Both black and brown stones, as well as calcified cholesterol stones, do not dissolve readily with ursodeoxycholic acid treatment.

12. Answer d
This patient's symptoms are nonspecific and not likely to be due to her gallstones. Her lifetime risk of symptoms is about 20%, with the risk of a more serious event (cholecystitis, choledocholithiasis, or pancreatitis) much less than 1% per year. In the absence of biliary symptoms, diabetes mellitus does not merit elective cholecystectomy.

13. Answer a
The clinical scenario and increased bilirubin level strongly suggest a bile duct leak, and the normal ERCP findings suggest injury to an anomalous bile duct not detected with ERCP, such as a right posterior segment duct draining into the extrahepatic tree or near the cystic duct (or both).

14. Answer b
This patient most likely has macroamylasemia, associated with a low amylase clearance in urine because of its association with a macroglobulin in serum. Serum levels of amylase can be more than tenfold normal. This is not a common disorder.

15. Answer e
This patient's history, including his family history, strongly suggests the autosomal dominant disorder of hereditary pancreatitis; hence, genetic counseling and testing for cationic trypsinogen gene mutation should be performed. Although the risk of pancreatic cancer is high, there are no effective screening methods. Conservative management and smoking cessation would be recommended, given his infrequent episodes of acute pain.

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About the book…

Written by an experienced and dedicated team of Mayo Clinic gastroenterologists and hepatologists, this newly expanded and updated *Third Edition* of the best-selling *Mayo Clinic Gastroenterology and Hepatology Board Review* is the go-to comprehensive resource for a complete scope of essential knowledge in all areas of gastroenterology and hepatology and in the related areas of pathology, endoscopy, nutrition, and radiology.

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- An abundance of additional new material appropriate for the board review and practice

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