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FIGURE 333-65 Virtual colonoscopy image of a colon polyp (arrow). (Image courtesy of Dr. Jeff Fidler; with permission.) FIGURE 333-66 Crohn’s ileitis. Edema, erythema, ulcers, and exudates involving the terminal ileum. FIGURE 333-67 Internal hemorrhoids with bleeding stigmata (arrow) as seen on retroflexed view of the rectum.

■ ■FURTHER READING Ahmed O et al: AGA clinical practice update on the optimal manage

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Esophagus CHAPTER 334 Diseases of the Esophagus ESOPHAGEAL STRUCTURE AND FUNCTION The esophagus is a hollow, muscular tube coursing through the pos terior mediastinum joining the hypopharynx to the stomach with a sphincter at each end. It functions to transport food and fluid between these ends, otherwise remaining empty. The physiology of swallowing, esophageal motility, and oral and pharyngeal dysphagia are described in Chap. 47. Esophageal diseases can be manifested by impaired func tion or pain. Key functional impairments are swallowing disorders and excessive gastroesophageal reflux. Pain, sometimes indistinguishable from cardiac chest pain, can result from inflammation, infection, dys motility, or neoplasm. SYMPTOMS OF ESOPHAGEAL DISEASE The clinical history remains central to the evaluation of esophageal symptoms. A thoughtfully obtained history will often expedite manage ment. Important details include weight gain or loss, gastrointestinal bleeding, dietary habits including the timing of meals, smoking, and alcohol consumption. The major esophageal symptoms are heartburn, regurgitation, chest pain,

dysphagia, odynophagia, and globus sensation. Heartburn (pyrosis), the most common esophageal symptom, is characterized by a discomfort or burning sensation behind the ster num that arises from the epigastrium and may radiate toward the neck. Heartburn is usually an intermittent symptom, most commonly experienced after eating, during exercise, and while lying recumbent. The discomfort is relieved with drinking water or taking an antacid but can occur frequently, interfering with normal activities including sleep. The association between heartburn and gastroesophageal reflux dis ease (GERD) is so strong that empirical therapy for GERD has become accepted management. However, the term heartburn is often misused and/or referred to using other terms such as indigestion or repeating, making it important to clarify the intended meaning. *Deceased.

Regurgitation is the effortless return of food or fluid into the phar ynx without nausea or retching. Patients report a sour or burning fluid in the throat or mouth that may also contain undigested food par ticles. Bending, belching, or maneuvers that increase intraabdominal pressure can provoke regurgitation. A clinician needs to discriminate among regurgitation, vomiting, and rumination. Vomiting is preceded by nausea and accompanied by retching. Rumination is a behavior in which recently swallowed food is regurgitated and then reswallowed repetitively for up to an hour. Although there is some linkage between rumination and cognitive deficiency, the behavior is also exhibited by unimpaired individuals.

Chest pain is a common esophageal symptom with characteristics similar to cardiac pain, sometimes making this distinction difficult. Esophageal pain is usually experienced as a pressure-type sensation in the mid chest, radiating to the mid back, arms, or jaws. The similarity to cardiac pain is likely because the two organs share a nerve plexus and the nerve endings in the esophageal wall have poor discriminative ability among stimuli. Esophageal distention or even chemostimulation (e.g., with acid) will often be perceived as chest pain. Gastroesophageal reflux is the most common cause of esophageal chest pain. Esophageal dysphagia (Chap. 47) is often described as a feeling of food “sticking” or even lodging in the chest. Important distinctions are between uniquely solid food dysphagia as opposed to liquid and solid, episodic versus constant dysphagia, and progressive versus static dys phagia. If the dysphagia is for liquids as well as solid food, it suggests a motility disorder such as achalasia. Conversely, uniquely solid food dysphagia is suggestive of a stricture, web, ring, or tumor. Of note, a patient’s localization of food hang-up in the esophagus is notoriously imprecise. Approximately 30% of distal esophageal obstructions are perceived as cervical dysphagia. In such instances, the absence of con comitant symptoms generally associated with oropharyngeal dysphagia such as aspiration, nasopharyngeal regurgitation, cough, drooling, or obvious neuromuscular compromise should suggest an esophageal etiology. PART 10 Disorders of the Gastrointestinal System Odynophagia is pain either caused by or exacerbated by swallowing. Although typically considered distinct from dysphagia, odynophagia may manifest concurrently with dysphagia. Odynophagia is more common with pill or infectious esophagitis than with reflux esophagitis and should prompt a search for these entities. When odynophagia does occur in GERD, it is likely related to an esophageal ulcer or extensive erosions. Globus sensation, also known as globus pharyngeus, is the per ception of a lump or fullness in the throat that is felt irrespective of swallowing. Although such patients are frequently referred for an evaluation of dysphagia, globus sensation is often relieved by the act of swallowing. As implied by its alternative name, “globus hystericus,” globus sensation often occurs in the setting of anxiety or obsessivecompulsive disorders. Clinical experience teaches that it is often attrib

utable to GERD. Water brash is excessive salivation resulting from a vagal reflex trig gered by acidification of the esophageal mucosa. This is not a common symptom. Afflicted individuals will describe the unpleasant sensation of the mouth rapidly filling with salty thin fluid, often in the setting of concomitant heartburn. DIAGNOSTIC STUDIES ■ ■ENDOSCOPY Endoscopy, also known as esophagogastroduodenoscopy (EGD), is the most useful test for the evaluation of the proximal gastrointesti nal tract. Modern instruments produce high-quality, color images of the esophageal, gastric, and duodenal lumen. Endoscopes also have an instrumentation channel through which biopsy forceps, injection catheters for focal delivery of therapeutic agents, balloon dilators, or devices for hemostasis or removal of mucosal lesions can be used. The key advantages of endoscopy over barium radiography are as fol lows: (1) increased sensitivity for the detection of mucosal lesions; (2) vastly increased sensitivity for the detection of abnormalities mainly identifiable by color, such as Barrett’s metaplasia or vascular lesions;

(3) the ability to obtain biopsy specimens for histologic examination of suspected abnormalities; and (4) the ability to dilate strictures during the examination. Submucosal (“third space”) endoscopy has emerged as a diagnostic modality for assessment of subepithelial lesions, resec tion of superficial dysplastic areas, and therapy of esophageal motility disorders. The main disadvantages of endoscopy are low sensitivity for detection of very proximal esophageal strictures or narrow caliber esophagus without focal stricturing, cost, and the need for sedatives or anesthetics. ■ ■RADIOGRAPHY Contrast radiography of the esophagus, stomach, and duodenum can demonstrate reflux of the contrast media, hiatal hernia, mucosal granularity, erosions, ulcerations, and strictures. The sensitivity of radiography compared with endoscopy for detecting reflux esophagitis reportedly ranges from 22 to 95%, with higher grades of esophagitis (i.e., ulceration or stricture) exhibiting greater detection rates. Con versely, the sensitivity of barium radiography for detecting esophageal strictures is greater than that of endoscopy, especially when the study is done in conjunction with a 13-mm barium tablet. Barium studies also provide an assessment of esophageal function and morphology that may be undetected on endoscopy. Tracheoesophageal fistula, altered postsurgical anatomy, and extrinsic esophageal compression are conditions where radiographic imaging complements endoscopic assessment. Hypopharyngeal pathology and disorders of the cricopha ryngeus muscle are better appreciated on radiographic examination than with endoscopy, particularly with rapid sequence or video fluoro scopic recording. The major shortcoming of barium radiography is that it rarely obviates the need for endoscopy. Either a positive or a negative study is usually followed by an endoscopic evaluation to obtain biop sies, provide therapy, clarify findings in the case of a positive examina tion, or add a level of certainty in the case of a negative examination. ■ ■ENDOSCOPIC ULTRASOUND Endoscopic ultrasound (EUS) instruments combine an endoscope with an ultrasound transducer to create a transmural image of the tissue sur rounding the endoscope tip. The key advantage of EUS over alternative radiologic imaging techniques is much greater resolution attributable to the proximity of the ultrasound transducer to the area being exam ined. Available devices can provide either radial imaging (360-degree, cross-sectional) or a curved linear image that can guide fine-needle aspiration of imaged structures such as lymph nodes or tumors. Major esophageal applications of EUS are to stage esophageal cancer, to evalu ate dysplasia in Barrett’s esophagus, and to assess submucosal lesions. ■ ■ESOPHAGEAL MANOMETRY Esophageal manometry, or motility testing, entails positioning a cath eter with multiple pressure sensors within the esophagus and then observing the contractility following test swallows. The upper esopha geal sphincter and lower esophageal sphincter (LES) appear as zones of high pressure that relax on swallowing,

whereas the intersphinc teric esophagus exhibits peristaltic contractions. Manometry is used to diagnose motility disorders (achalasia, diffuse esophageal spasm [DES]) and to assess peristaltic integrity prior to the surgery for reflux disease. Technologic advances have enhanced esophageal manom etry as high-resolution esophageal pressure topography (Fig. 334-1). Manometry can also be combined with intraluminal impedance moni toring. Impedance recordings use a series of paired electrodes added to the manometry catheter. Esophageal luminal contents in contact with the electrodes decrease (liquid) or increase (air) the impedance signal, allowing detection of anterograde or retrograde esophageal bolus transit. ■ ■FUNCTIONAL LUMEN IMAGING PROBE The functional lumen imaging probe (FLIP) is a catheter-based tech nology that utilizes high-resolution impedance planimetry during volume-controlled esophageal distension to measure esophageal crosssectional area and distensibility (i.e., cross-sectional area in relation to distension pressure) along a 16-cm length of the esophagus. These data

FIGURE 334-1 High-resolution esophageal pressure topography (left) and conventional manometry (right) of a normal swallow. E, esophageal body; LES, lower esophageal sphincter; UES, upper esophageal sphincter. are displayed in real time on a computer monitor both as a cylinder of varied diameter along the 16-cm length of the probe or as real-time diameter topography akin to high-resolution manometry. FLIP studies are performed with sedation in conjunction with upper endoscopy or intraoperatively; the probe is passed transorally. Assessing esophageal motility with FLIP is based on quantifying esophagogastric junction opening during volumetric distention and characterizing distensioninduced esophageal contractility, which is, in essence, secondary peri stalsis. These findings are classified according to a scheme known as FLIP panometry. There is excellent correlation between FLIP panom etry and high-resolution manometry in the detection of both achalasia and normal contractility, the two most important potential findings. Hence, FLIP can be used to evaluate patients with esophageal dyspha gia, often in lieu of manometry. REFLUX TESTING GERD is often diagnosed in the absence of endoscopic signs of esopha gitis, which would otherwise define the disease. This occurs in the settings of partially treated disease, an abnormally sensitive esophageal mucosa, or, most commonly, in nonerosive reflux disease. In such instances, reflux testing can demonstrate excessive esophageal expo sure to refluxed gastric fluid, the physiologic abnormality of GERD. This can be done by ambulatory 24- to 96-h esophageal pH recording using either a wireless pH-sensitive transmitter that is affixed to the esophageal mucosa or a transnasally positioned wire electrode with the tip stationed in the distal esophagus. Either way, the outcome is expressed as the percentage of the day that the pH was <4 (indicative of recent acid reflux), with values exceeding 6% indicative of GERD. Reflux testing is useful in the evaluation of patients presenting with atypical symptoms or an inexplicably poor response to therapy. Intralu minal impedance monitoring can be added to pH monitoring to detect reflux events irrespective of whether or not they are acidic, potentially increasing the sensitivity of the study. STRUCTURAL DISORDERS ■ ■HIATAL HERNIA Hiatal hernia is a herniation of viscera, most commonly the stomach, into the mediastinum through the esophageal hiatus of the diaphragm. Four types of hiatal hernia are distinguished, with type I, or sliding hiatal hernia, comprising about 95% of the overall total. A sliding hiatal hernia is one in which the gastroesophageal junction and gastric cardia translocate cephalad as a result of weakening of the phrenoesophageal ligament attaching the gastroesophageal junction to the diaphragm at the hiatus and dilatation of the diaphragmatic hiatus. The incidence of sliding hernia increases with age. True to its name, sliding hernias enlarge with increased intraabdominal pressure, swallowing, and res piration. Conceptually, sliding hernias are the result of wear and tear: increased intraabdominal pressure from abdominal

obesity, pregnancy,

etc., along with hereditary factors predisposing to the condition. The main significance of sliding hernias is the propensity of affected indi viduals to develop GERD. Type II, III, and IV hiatal hernias are all subtypes of paraesophageal hernia in which there is herniation into the mediastinum of viscera above the gastric cardia. With type II and III paraesophageal hernias, the gastric fundus herniates, with the distinction being that in type II, the gastroesophageal junction remains fixed at the hiatus, whereas type III is a combined sliding and paraesophageal hernia. With type IV hiatal hernias, viscera other than the stomach herniate into the mediasti num, most commonly the colon. With type II and III paraesophageal hernias, the stomach progressively inverts as it herniates, and large paraesophageal hernias can lead to an “upside down stomach,” gastric volvulus, and even strangulation of the stomach. Because of this risk, surgical repair is often advocated for large paraesophageal hernias, particularly when they are symptomatic. CHAPTER 334 Diseases of the Esophagus ■ ■RINGS AND WEBS A lower esophageal mucosal ring, also called a B ring, is a thin membra nous narrowing at the squamocolumnar mucosal junction (Fig. 334-2). Tubular esophagus Esophageal vestibule Phrenic ampulla Sliding hiatal hernia A ring B ring squamo-columnar junction Rugal folds traversing hiatus Diaphragmatic impression FIGURE 334-2 Radiographic anatomy of the gastroesophageal junction.

Its origin is unknown, but B rings are demonstrable in ~10–15% of the general population and are usually asymptomatic. When the lumen diameter is <13 mm, distal rings are usually associated with episodic solid food dysphagia and are called Schatzki rings. Patients typically present older than 40 years, consistent with an acquired rather than congenital origin. Schatzki ring is a common cause of intermittent food impaction, also known as “steakhouse syndrome” because meat is a typical instigator. Symptomatic rings are readily treated by dilation.

Web-like constrictions higher in the esophagus can be of congeni tal or inflammatory origin. Asymptomatic cervical esophageal webs are demonstrated in ~10% of people and typically originate along the anterior aspect of the esophagus. Depending on the degree of impingement, they can cause intermittent dysphagia to solids similar to Schatzki rings and are similarly treated with dilation. The combination of symptomatic proximal esophageal webs and iron-deficiency anemia in middle-aged women constitutes Plummer-Vinson or Paterson-Kelly syndrome. ■ ■DIVERTICULA Esophageal diverticula are categorized by location, with the most com mon being epiphrenic, hypopharyngeal (Zenker’s), and midesopha geal. Epiphrenic and Zenker’s diverticula are false diverticula involving herniation of the mucosa and submucosa through the muscular layer of the esophagus. These lesions result from increased intraluminal pressure associated with distal obstruction. In the case of Zenker’s, the obstruction is a stenotic cricopharyngeus muscle (upper esophageal sphincter), and the hypopharyngeal herniation occurs in an area of natural weakness proximal to the cricopharyngeus known as Killian’s triangle (Fig. 334-3). Small Zenker’s diverticula are usually asymptom atic, but when they enlarge sufficiently to retain food and saliva, they can be associated with dysphagia, halitosis, and aspiration. Treatment is by surgical diverticulectomy and cricopharyngeal myotomy or tran soral, endoscopic myotomy. PART 10 Disorders of the Gastrointestinal System Epiphrenic diverticula are often associated with achalasia or esopha geal hypercontractile disorders. Midesophageal diverticula may be caused by traction from adjacent inflammation (tuberculosis, histo plasmosis), in which case they are true diverticula involving all lay ers of the esophageal wall, or by pulsion associated with esophageal motility disorders.

Midesophageal and epiphrenic diverticula are often asymptomatic; symptoms tend to correlate more with the underlying esophageal disorder. Large epiphrenic diverticula can be removed surgically, usually in conjunction with a myotomy. Diffuse intramural esophageal pseudodiverticulosis is a rare entity resulting from dilata tion of the excretory ducts of submucosal esophageal glands (Fig. 334-4). A B C FIGURE 334-3 Examples of small (A) and large (B, C) Zenker's diverticula arising from Killian's triangle in the distal hypopharynx. Smaller diverticula are evident only during the swallow, whereas larger ones retain food and fluid.

FIGURE 334-4 Intramural esophageal pseudodiverticulosis associated with chronic obstruction. Invaginations of contrast into the esophageal wall outline deep esophageal glands. Esophageal candidiasis or strictures are commonly found in associa tion with pseudodiverticulosis. ■ ■TUMORS The American Cancer Society's 2023 estimates for esophageal can cer in the United States are about 21,560 new cases (79% men) and

16,120 deaths. It is ~7 times less common than colorectal cancer but kills about a third as many patients, emphasizing both the rarity and lethality of esophageal cancer. One notable trend is the shift of domi nant esophageal cancer type from squamous cell to adenocarcinoma, strongly linked to reflux disease and Barrett's metaplasia. Other dis tinctions between cell types are the predilection for adenocarcinoma to affect the distal esophagus in white males and for squamous cell carcinoma to affect the more proximal esophagus in black males with the added risk factors of smoking, alcohol consumption, caustic injury, and human papillomavirus infection (Chap. 85). The typical presentation of esophageal cancer is of progressive solid food dysphagia and weight loss. Associated symptoms may include odynophagia, iron deficiency, cough from tracheoesophageal fistula, and hoarseness from left recurrent laryngeal nerve injury. Generally, respiratory symptoms are manifestations of locally invasive or even metastatic disease. Even when detected as a small lesion, esophageal cancer has poor survival because of the abundant esophageal lymphat ics leading to early regional lymph node metastases. Benign esophageal tumors are uncommon and usually discovered incidentally. They include gastrointestinal stromal tumors, leiomyoma, fibrovascular polyps, squamous papilloma, granular cell tumors, lipo mas, mesenchymal neoplasms, and inflammatory fibroid polyps. CONGENITAL ANOMALIES The most common congenital esophageal anomaly is esophageal atresia, occurring in ~2.5 per 10,000 live births. Atresia can occur in several permutations, the common denominator being developmental failure of fusion between the proximal and distal esophagus associated with a tracheoesophageal fistula, most commonly with the distal seg ment excluded. Alternatively, there can be an H-type configuration in which esophageal fusion has occurred, but with a tracheoesophageal fistula. Esophageal atresia is usually recognized and corrected surgi cally within the first few days of life. Later life complications include dysphagia from anastomotic strictures or absent peristalsis and reflux, which can be severe. Less common developmental anomalies include congenital esophageal stenosis, webs, and duplications. Dysphagia can also result from vascular congenital abnormalities that cause extrinsic compression of the esophagus, a condition called dysphagia lusoria. Most commonly, the esophagus is compressed by an aberrant right subclavian artery arising from the descending aorta and passing behind the esophagus. Alternatively, vascular rings may sur round and constrict the esophagus. Heterotopic gastric mucosa, also known as an esophageal inlet patch, is a focus of gastric-type epithelium in the proximal cervi cal esophagus; the estimated prevalence is 4–5%. The inlet patch is thought to result from incomplete replacement of embryonic columnar epithelium with squamous epithelium. The majority of inlet patches are asymptomatic, but acid

production along with associated symp toms and even ulceration can occur as most contain fundic-type gastric epithelium with parietal cells. ESOPHAGEAL MOTILITY DISORDERS Esophageal motility disorders are diseases attributable to abnormal esophageal neuromuscular dysfunction commonly associated with dysphagia, chest pain, or heartburn. The major entities are achalasia, distal esophageal spasm (DES), and GERD. Motility disorders can also be secondary to systemic disease processes, as is the case with pseu doachalasia, Chagas' disease, and scleroderma. Not included in this discussion are diseases affecting the pharynx and proximal esophagus, the impairment of which is almost always part of a more global neuro muscular disease process. ■ ■ACHALASIA Achalasia is a rare disease with a population incidence estimated to be 1–3 per 100,000 and presentation usually occurring between age 25 and 60 years. Although there is some degree of heterogeneity in its pathogenesis, the classic cases are caused by autoimmune-mediated death of ganglion cells within the esophageal myenteric plexus; with long-standing disease, aganglionosis is noted. The disease involves

both excitatory (cholinergic) and inhibitory (nitric oxide) ganglionic neurons, which mediate deglutitive LES relaxation and the sequential propagation of peristalsis. Their absence leads to impaired deglutitive LES relaxation and absent peristalsis. Increasing evidence suggests that the ultimate cause of ganglion cell degeneration in achalasia is an auto immune process attributable to a latent infection with human herpes simplex virus 1 combined with genetic susceptibility.

Long-standing achalasia is characterized by progressive dilatation and sigmoid deformity of the esophagus, sometimes associated with hypertrophy of the LES. Clinical manifestations may include dysphagia, regurgitation, chest pain, and weight loss. Most patients report solid and liquid food dysphagia. Regurgitation occurs when food, fluid, and secretions are retained in the dilated esophagus. Patients with advanced achalasia are at risk for bronchitis, pneumonia, or lung abscess from chronic regurgitation and aspiration. Chest pain may manifest early in the course of achalasia. Patients describe a squeezing, pressure-like retrosternal pain, sometimes radiating to the neck, arms, jaw, and back. Paradoxically, some patients complain of heartburn that may be a chest pain equivalent. Treatment of achalasia is less effective at alleviating chest pain than it is in relieving dysphagia or regurgitation. The differential diagnosis of achalasia includes DES, Chagas' dis ease, opioid-induced esophageal dysmotility, and pseudoachalasia. Chagas' disease is endemic in areas of central Brazil, Venezuela, and northern Argentina and spread by the bite of the reduviid (kissing) bug that transmits the protozoan Trypanosoma cruzi. The chronic phase of the disease develops years after infection and results from destruc tion of autonomic ganglion cells throughout the body, including the heart, gut, urinary tract, and respiratory tract. Manometric features of achalasia have been described in patients on chronic opioids and may be confused with primary achalasia. Tumor infiltration, most com monly seen with carcinoma in the gastric cardia or distal esophagus, can also mimic primary achalasia. The resultant "pseudoachalasia" accounts for up to 5% of suspected cases and is more likely with advanced age, abrupt onset of symptoms (<1 year), and weight loss. Hence, endoscopy is a necessary part of the evaluation of achalasia. When the clinical suspicion for pseudoachalasia is high and endoscopy is nondiagnostic, computed tomography (CT) scanning or EUS may be of value. Rarely, pseudoachalasia can result from a paraneoplastic syndrome with circulating antineuronal antibodies. CHAPTER 334 Diseases of the Esophagus Achalasia is diagnosed by barium swallow x-ray and/or esopha geal manometry. Endoscopy excludes tumors or benign mechanical strictures of the esophagogastric junction. The barium swallow x-ray appearance is of a dilated esophagus with poor emptying, an air-fluid level, and tapering at the LES

giving it a beak-like appearance (Fig. 334-5). Occasionally, an epiphrenic diverticulum is observed. In longstanding achalasia, the esophagus may assume a sigmoid configura tion. The diagnostic criteria for achalasia with esophageal manometry FIGURE 334-5 Achalasia with esophageal dilatation, tapering at the gastroesophageal junction, and an air-fluid level within the esophagus. The example on the left shows sigmoid deformity with very advanced disease.

A. Classic achalasia 0 Pharynx

cm

–10

mmHg 35 Stomach

Seconds B. Achalasia with compression

0 Pharynx

cm

–5

35 Stomach –10 mmHg

PART 10 Disorders of the Gastrointestinal System Seconds mmHg C. Spastic achalasia

0 Pharynx

cm

35 Stomach –10

Seconds FIGURE 334-6 Three subtypes of achalasia: classic (A), with esophageal compression (B), and spastic achalasia (C) imaged with high-resolution manometry. All are characterized by impaired lower esophageal sphincter (LES) relaxation and absent peristalsis. However, classic achalasia has minimal pressurization of the esophageal body, whereas substantial fluid pressurization is observed in achalasia with esophageal compression, and spastic esophageal contractions are observed with spastic achalasia. are impaired LES relaxation and absent peristalsis. High-resolution manometry has somewhat advanced this diagnosis; three subtypes of achalasia are differentiated based on the pattern of pressurization in the nonperistaltic esophagus (Fig. 334-6). Because manometry identifies early disease before esophageal dilatation and food retention, it is the most sensitive diagnostic test. No method of preventing or “curing” achalasia is known. Therapy is thus directed at reducing LES pressure so that gravity and esophageal pressurization permit esophageal emptying. While peristalsis does not recover, remnants of peristalsis masked by esophageal pressuriza tion and dilatation prior to therapy may be demonstrable following effective treatment. LES pressure can be reduced by pharmacologic therapy, pneumatic balloon dilation, or LES myotomy by means of submucosal (third space)

endoscopy or laparoscopic surgery.

Pharmacologic therapies are relatively ineffective but can be offered as temporizing therapies. Nitrates or calcium channel blockers are administered before eating but should be used with caution because of their effects on blood pressure. Botulinum toxin, injected into the LES under endoscopic guidance, inhibits acetylcholine release from nerve endings and improves dysphagia in about two-thirds of cases for at least 6 months. Sildenafil and alternative phosphodiesterase inhibitors effectively decrease LES pressure, but practicalities limit their clinical use in achalasia. The only durable therapies for achalasia are pneumatic dilation and LES myotomy. Pneumatic dilation, with a reported efficacy ranging widely from 60 to 90%, is an endoscopic technique using a noncompli ant, cylindrical balloon dilator positioned across the LES and inflated to a diameter of 3–4 cm. The major complication is perforation, with a reported incidence of 0.5–5%. The most common surgical procedure for achalasia is laparoscopic Heller myotomy, usually performed in conjunction with an antireflux procedure (partial fundoplication); good to excellent results are reported in 62–90% of cases. A European randomized controlled trial demonstrated an equivalent response rate of ~90% for both pneumatic dilation and laparoscopic Heller myotomy at 5-year follow-up. Occasionally, patients with advanced disease fail to respond to pneumatic dilation or Heller myotomy or relapse years after response to primary therapy. In such refractory cases, esophageal resection with gastric pull-up or interposition of a segment of trans verse colon may be the only option other than gastrostomy feeding. An endoscopic approach to LES myotomy is increasingly available, referred to as peroral endoscopic (or esophageal) myotomy (POEM). This technique involves endoscopically incising the esophageal mucosa and creating a tunnel in the submucosa of the esophageal wall through which the circular muscle of the LES and a calibrated length of distal esophagus are transected with electrocautery. GERD is common after POEM but managed effectively with medications. Potential advantages over the conventional laparoscopic approach include avoidance of surgical disruption of the diaphragmatic hiatus and more rapid recov ery. An international, multicenter, randomized trial of POEM and pneumatic dilation demonstrated greater symptom relief with POEM compared to dilation at 2 and 5 years. A European, multicenter, ran domized trial of POEM and Heller myotomy reported similar efficacy for symptom relief, exceeding 80% with either. In untreated or inadequately treated achalasia, esophageal dilatation predisposes to stasis esophagitis. Prolonged stasis esophagitis is the likely explanation for the association between achalasia and esophageal squamous cell cancer. Tumors develop after years of achalasia, usually in the setting of extreme esophageal dilatation, with the overall squa mous cell cancer risk increased 17-fold compared to controls. ■ ■DISTAL ESOPHAGEAL SPASM DES is manifest by episodes of dysphagia and chest pain attribut able to abnormal esophageal contractions with normal deglutitive LES relaxation. The pathophysiology and natural history of DES are poorly defined. Radiographically, DES has been characterized by tertiary contractions or a “corkscrew esophagus” (Fig. 334-7), but in many instances, these abnormalities are indicative of achalasia. Mano metrically, a variety of defining features have been proposed including uncoordinated (“spastic”) activity in the distal esophagus, spontaneous and repetitive contractions, or high-amplitude and prolonged contrac tions. High-resolution manometry has defined DES by the occurrence of contractions in the distal esophagus with short latency relative to the time of the pharyngeal contraction, a dysfunction indicative of impair ment of inhibitory myenteric plexus neurons. When defined with this restrictive criterion (Fig. 334-8), DES is substantially less common than achalasia. Esophageal chest pain closely mimics angina pectoris. Features sug gesting esophageal pain include pain that is nonexertional, prolonged, meal-related,

relieved with antacids, accompanied by heartburn, dys phagia, or regurgitation, and interrupts sleep. However, all of these fea tures exhibit overlap with cardiac pain, which still must be the primary consideration. Furthermore, even within the spectrum of esophageal diseases, both chest pain and dysphagia are also characteristic of peptic

FIGURE 334-7 Distal esophageal spasm. The characteristic “corkscrew” esophagus results from spastic contraction of the circular muscle in the esophageal wall; more precisely, this is actually a helical array of muscle. These findings are also seen with spastic achalasia. or infectious esophagitis. Only after these more common entities have been excluded by evaluation and/or treatment should a diagnosis of DES be pursued. Although DES is diagnosed by manometry, endoscopy is useful to identify alternative structural and inflammatory lesions that may cause chest pain. Radiographically, a “corkscrew esophagus,” “rosary bead esophagus,” pseudodiverticula, or curling can be indicative of DES, but these are also found with spastic achalasia. Given these vagaries of defining DES and the resultant heterogeneity of patients identified for inclusion in therapeutic trials, it is not surprising that trial results have been disappointing. Only small, uncontrolled trials exist, reporting response to nitrates, calcium channel blockers, hydralazine, botulinum toxin, and anxiolytics. POEM with distal esophageal myotomy or sur gical myotomy should be considered only with severe weight loss or intractable pain. These indications are extremely rare. ■ ■NONSPECIFIC MANOMETRIC FINDINGS Manometric studies done to evaluate chest pain and/or dysphagia often report minor abnormalities (e.g., hypertensive or hypotensive peristalsis, hypertensive LES) that are insufficient to diagnose either

mmHg Jackhammer esophagus

Time (s) Time (s) Normal latency with hypercontractility

Short latency, premature contraction FIGURE 334-8 Esophageal pressure topography of the two major variants of esophageal spasm: hypercontractile esophagus (left) and distal esophageal spasm (right). Hypercontractile esophagus is defined by the extraordinarily vigorous, sometimes repetitive contractions with normal peristaltic onset and normal latency of the contraction. Distal esophageal spasm is similar but primarily defined by a short latency (premature) contraction.

achalasia or DES. These findings are of unclear significance. Reflux and psychiatric diagnoses, particularly anxiety and depression, are common among such individuals. A lower visceral pain threshold and symptoms of irritable bowel syndrome are noted in more than half of such patients. Consequently, therapy for these individuals should tar get either the most common esophageal disorder, GERD, or cognitive disorders that may be present.

GASTROESOPHAGEAL REFLUX DISEASE The current concept of GERD is that it encompasses a family of conditions with the commonality that they are caused by gastro esophageal reflux resulting in either troublesome symptoms or an array of potential esophageal and extraesophageal manifestations. It is estimated that 10–15% of adults in the United States are affected by GERD, although such estimates are based on population studies of self-reported chronic heartburn. With respect to the esophagus, the spectrum of injury includes esophagitis, stricture, Barrett’s esophagus, and adenocarcinoma (Fig. 334-9). Of particular concern is the rising incidence of esophageal adenocarcinoma, an epidemiologic trend that parallels the increasing incidence of

GERD. About 9200 incident cases of esophageal adenocarcinoma were noted in the United States in 2020 (estimated as half of all esophageal cancers); this disease burden has increased sixfold in the past 20 years. ■ ■PATHOPHYSIOLOGY The best-defined subset of GERD patients, albeit a minority overall, have esophagitis. Esophagitis occurs when refluxed gastric acid and pepsin induce inflammation of the esophageal mucosa that leads to microscopic injury and macroscopic erosions or ulcers. Experimental evidence supports a cytokine-mediated inflammatory pathway rather than direct caustic injury to the esophageal epithelium. Note that some degree of gastroesophageal reflux is normal, physiologically inter twined with the mechanism of belching (transient LES relaxation), but esophagitis results from excessive reflux, often accompanied by impaired clearance/neutralization of the refluxed gastric juice. Restricting reflux to that which is physiological levels depends on the anatomic and physiologic integrity of the esophagogastric junction, a complex valvular mechanism functionally dependent on the LES, the surrounding crural diaphragm, and the native subdiaphragmatic endto-side architecture of the gastroesophageal junction. Pathologic reflux is a consequence of the interplay between progressive anatomic distor tion of the native architecture of the gastroesophageal junction and physiology. Relevant factors include (1) widening of the diaphragmatic hiatus and diminished crural diaphragm sphincteric function; (2) loss of an intraabdominal esophageal segment with complete disabling of the native flap valve architecture; (3) axial hiatus hernia, which causes CHAPTER 334 Diseases of the Esophagus LES hypotension and loss of the ability to prevent reflux during swallow-induced LES relaxation, inspiration, or straining; and (4) increased compliance of gastroesopha geal junction leading to wider sphincter opening during transient LES relaxations (the belch reflex) with loss of the ability to prevent liquid escaping along with the gas. Factors tending to exacerbate reflux regard less of mechanism are abdominal obesity, pregnancy, gastric hypersecretory states, delayed gastric emptying, disruption of esophageal peristalsis, and gluttony. Diffuse esophageal spasm Latency= 3.5 s After acid reflux, peristalsis returns the refluxed fluid to the stomach, and acid clearance is completed by titration of the residual acid by bicarbonate contained in swallowed saliva. Consequently, two causes of prolonged acid clearance are impaired peristalsis and reduced salivation. Impaired peristaltic emptying can be attributable to disrupted peristalsis or superimposed reflux associated with a hiatal hernia. With

Esophageal stricture with chronic erosive esophagitis A B Erosive esophagitis PART 10 Disorders of the Gastrointestinal System Barrett’s esophagus Esophageal adenocarcinoma with Barrett’s esophagus C D FIGURE 334-9 Endoscopic appearance of (A) peptic esophagitis, (B) a peptic stricture, (C) Barrett’s metaplasia, and (D) adenocarcinoma developing within an area of Barrett’s esophagus. superimposed reflux, fluid retained within a sliding hiatal hernia refluxes back into the esophagus during swallow-related LES relax ation, a phenomenon that does not normally occur. Inherent in the pathophysiologic model of GERD is that gastric juice is harmful to the esophageal epithelium. However, gastric acid hypersecretion is usually not a dominant factor in the development of esophagitis. An obvious exception is with Zollinger-Ellison syn drome, which is associated with severe esophagitis in ~50% of patients. Another caveat is with chronic Helicobacter pylori gastritis, which may have a protective effect by inducing atrophic gastritis with concomitant hypoacidity. Pepsin, bile, and pancreatic enzymes within gastric secre tions can also injure the esophageal epithelium, but their noxious prop erties are either lessened without an acidic environment or dependent on acidity for activation. Bile warrants attention because it persists in refluxate despite acid-suppressing medications. Bile can traverse the cell membrane, imparting severe cellular injury in a weakly acidic envi ronment, and has also been invoked as a

cofactor in the pathogenesis of Barrett’s metaplasia and adenocarcinoma. Hence, the causticity of gastric refluxate extends beyond hydrochloric acid. ■ ■SYMPTOMS Heartburn and regurgitation are the typical symptoms of GERD. Somewhat less common are dysphagia and chest pain. In each case, multiple potential mechanisms for symptom genesis operate that extend beyond the basic concepts of mucosal erosion and activation of afferent sensory nerves. Specifically, visceral hypersensitivity is increas ingly recognized as a cofactor. Nonetheless, the dominant clinical strategy is empirical treatment with acid inhibitors, reserving further evaluation for those who fail to respond. Important exceptions to this are patients with chest pain or persistent dysphagia, each of which may be indicative of GERD or alternative diagnoses. With chest pain, car diac disease must be considered. With dysphagia, eosinophilic esopha gitis (EoE) should be considered as an alternative diagnosis along with peptic stricture, motility disorders, or esophageal cancer.

Extraesophageal syndromes associated with GERD include chronic cough, laryngitis, asthma, and dental erosions. Other conditions including pharyngitis, chronic bronchitis, pulmonary fibrosis, chronic sinusitis, cardiac arrhythmias, sleep apnea, and recurrent aspiration pneumonia have proposed associations with GERD. However, in both cases, it is important to emphasize the word association as opposed to causation. In many instances, the disor ders likely coexist without causality. Potential mech anisms for extraesophageal GERD manifestations are either regurgitation with direct contact between the refluxate and supraesophageal structures or via a vagovagal reflex wherein reflux activation of esopha geal afferent nerves triggers efferent vagal reflexes such as bronchospasm, cough, or arrhythmias. ■ ■DIFFERENTIAL DIAGNOSIS Although generally quite characteristic, symptoms from GERD need to be distinguished from symp toms related to infectious or pill esophagitis, EoE, peptic ulcer disease, dyspepsia, biliary colic, coronary artery disease, and esophageal motility disorders. It is especially important that coronary artery disease be given early consideration because of its potentially lethal implications. The remaining elements of the differential diagnosis can be addressed by endos copy, upper gastrointestinal series, or esophageal manometry as appropriate. Erosive esophagitis at the esophagogastric junction is the endoscopic hallmark of GERD, but it is identified in only about one-third of GERD patients. The distinction among etiologies of esophagitis is readily made by endoscopic appear ance, but mucosal biopsies are necessary to evaluate for infectious or eosinophilic inflammation. In terms of endoscopic appearance, the ulcerations seen in peptic esophagitis are usually few and distal, whereas infectious ulcerations are numer ous, punctate, and diffuse. EoE characteristically exhibits multiple esophageal edema, rings, linear furrows, white punctate exudate, and strictures. Esophageal ulcerations from pill esophagitis are usually singular and deep at points of luminal narrowing, especially near the carina, with sparing of the distal esophagus. ■ ■COMPLICATIONS The complications of GERD are related to chronic esophagitis (bleed ing and stricture) and the relationship between GERD and esophageal adenocarcinoma. However, both erosive esophagitis and peptic stric tures have become increasingly rare in the era of potent antisecretory medications. Conversely, the most severe histologic consequence of GERD is Barrett’s metaplasia with the associated risk of esophageal adenocarcinoma, and the incidence of these lesions has increased, not decreased, in the era of potent acid suppression. Barrett’s metapla sia, recognized endoscopically by salmon-colored mucosa extending proximally from the gastroesophageal junction (Fig. 334-9) or his topathologically by the finding of intestinal metaplasia, is associated with a significantly increased risk for development of esophageal adenocarcinoma. Barrett’s metaplasia can progress to adenocarcinoma through the intermediate stages of low- and high-grade dysplasia (Fig. 334-10). Owing to this risk, areas of Barrett’s metaplasia and especially any

included areas of mucosal irregularity should be carefully inspected and extensively biopsied. The rate of cancer development is estimated at 0.1–0.3% per year, but vagaries in definitional criteria and of the extent of Barrett's metaplasia requisite to establish the diagnosis have contributed to variability and inconsistency in this risk assessment. The group at greatest risk is obese white males in their sixth decade of life. However, despite common practice, the utility of endoscopic screening and surveillance programs intended to control the adenocar cinoma risk remains an open question. Also of note, although in a large

Barrett's metaplasia High-grade dysplasia Alcian blue stain H&E stain FIGURE 334-10 Histopathology of Barrett's metaplasia and Barrett's metaplasia with high-grade dysplasia (arrows). H&E, hematoxylin and eosin. randomized, controlled trial of chemoprevention in Barrett's patients, high-dose proton pump inhibitor therapy along with aspirin did sig nificantly better at achieving the composite endpoint of delaying allcause mortality or Barrett's progression, the effect was driven mainly by improved overall survival rather than reduced Barrett's dysplasia or adenocarcinoma development. Although the management of Barrett's esophagus remains contro versial, the finding of dysplasia in Barrett's, particularly high-grade dysplasia, mandates further intervention. In addition to the high rate of progression to adenocarcinoma, there is also a high prevalence of unrecognized coexisting cancer with high-grade dysplasia. Treatment recommendations for Barrett's esophagus with high-grade dysplasia have evolved over the past several years. Historically, esophagectomy was the gold standard treatment for high-grade dysplasia. However, esophagectomy has a mortality ranging from 3 to 10%, along with substantial morbidity. Prospective studies have demonstrated the efficacy of endoscopic mucosal ablation therapy with substantially less morbidity and essentially no mortality. Consequently, current societal guidelines endorse endoscopic mucosal ablation therapies for the man agement of high-grade dysplasia. TREATMENT Gastroesophageal Reflux Disease Lifestyle modifications are routinely advocated as GERD therapy. Broadly speaking, these fall into three categories: (1) avoidance of foods that reduce LES pressure, making them "refluxogenic" (these commonly include fatty foods, alcohol, spearmint, pep permint, and possibly coffee and tea); (2) avoidance of acidic foods that are inherently irritating (citrus fruits, tomato-based foods); and (3) adoption of behaviors to minimize reflux and/or heartburn. In general, minimal evidence supports the efficacy of these measures. However, clinical experience dictates that subsets of patients benefit from specific recommendations based on their individual history and symptom profile. A patient with sleep dis turbance from nighttime heartburn is more likely to benefit from elevation of the head of the bed and avoidance of eating before retiring. The most broadly applicable recommendation is for weight reduction. Even though the benefit with respect to reflux cannot be assured, the strong epidemiologic relationship between body mass index and GERD and the secondary health gains of weight reduction is beyond dispute. The dominant pharmacologic approach to GERD management is with inhibitors of gastric acid secretion, and abundant data sup port the effectiveness of this approach. Pharmacologically reducing the acidity of gastric juice does not prevent reflux, but it ameliorates reflux symptoms and allows esophagitis to heal. The hierarchy of effectiveness among pharmaceuticals for healing esophagitis parallels their antisecretory potency. Potassium competitive acid blockers (PCABs) are more efficacious than proton pump inhibi tors (PPIs), which are more efficacious than histamine-2 receptor

antagonists (H2RAs). The differences are most evident with severe esophagitis, much less so with mild disease. Paradoxically, the perceived frequency and severity of heartburn correlate poorly

with the presence or severity of esophagitis. When GERD treatments are assessed in terms of resolving heartburn, both efficacy and differences among pharmaceuticals are less clear-cut than with the objective of healing esophagitis. Although the same overall hierarchy of effectiveness exists between PPIs and H2RAs (minimal data are available for PCABs), observed efficacy rates are lower and vary widely, likely reflecting patient heterogeneity. Reflux symptoms tend to be chronic, irrespective of esophagitis. Thus, a common management strategy is indefinite treatment with PPIs or H2RAs as necessary for symptom control. The side effects of PPI therapy are generally minimal. Rare cases of interstitial nephri tis and severe, reversible hypomagnesemia have been reported. Vitamin B12 and iron absorption may be compromised and suscep tibility to enteric infections, particularly Clostridioides difficile coli tis, increased with treatment. Observational data have also noted an association between PPI exposure and renal disease, dementia, and cardiovascular disease, but the hazard ratios reported in these studies were small, and the potential for unrecognized residual confounding bias was substantial. Population studies have also sug gested a slight increased risk of bone fracture with chronic PPI use suggesting an impairment of calcium absorption, but prospective studies have failed to corroborate this. Nonetheless, as with any medication, PPI dosage should be minimized to that necessary for the clinical indication. CHAPTER 334 Diseases of the Esophagus Laparoscopic fundoplication, wherein the proximal stomach is wrapped around the distal esophagus to create an antireflux bar rier, is a surgical alternative to the management of chronic GERD. Just as with PPI therapy, evidence on the utility of fundoplication is strongest for treating esophagitis, and controlled trials suggest similar efficacy to PPI therapy. However, the benefits of fundoplica tion must be weighed against potential deleterious effects, including surgical morbidity and mortality, postoperative dysphagia, failure or breakdown requiring reoperation, an inability to belch, and increased bloating, flatulence, and bowel symptoms after surgery. ■ ■EOSINOPHILIC ESOPHAGITIS EoE is increasingly recognized in adults and children around the world. Current prevalence estimates in the United States identified 4–8 cases per 10,000 with a predilection for white males between 30 and 40 years of age. The increasing prevalence of EoE is attributable to a combination of an increasing incidence and a growing recogni tion of the condition. There is also an incompletely understood, but important, interaction between EoE and GERD that may confound the diagnosis of the disease. Genome-wide analysis studies demonstrated susceptibility elements at 5q22 (thymic stromal lymphopoietin) and 2p23 (CAPN14) in EoE. EoE is diagnosed by the combination of esophageal symptoms and esophageal mucosal biopsies demonstrating eosinophil-predominant

inflammation. Alternative etiologies of esophageal eosinophilia include GERD, drug hypersensitivity, connective tissue disorders, hypereo sinophilic syndrome, Crohn’s disease, eosinophilic gastroenteritis, and infection. EoE is an immunologic disorder induced by antigen sensiti zation in susceptible individuals. Food allergens are the dominant trig gers, although aeroallergens may also contribute. The natural history of EoE is incompletely understood, but an increased risk of esophageal stricture development paralleling the duration of untreated disease has been noted.

EoE should be strongly considered in children and adults with dysphagia and esophageal food impactions. In preadolescent chil dren, symptom presentations of EoE include chest or abdominal pain, nausea, vomiting, and food aversion. Other symptoms in adults may include atypical chest pain and heartburn. An atopic history of IgE-mediated food allergy, asthma, eczema, and/or allergic rhinitis is present in the majority of patients. Peripheral blood eosinophilia is demonstrable in

25–50% of patients, but the specificity of this finding is problematic in the setting of concomitant atopy. The characteristic endoscopic esophageal findings include loss of vascular markings (edema), multiple esophageal rings, longitudinally oriented furrows, whitish exudate, and strictures (Fig. 334-11). Histologic confirmation is made with the demonstration of esophageal mucosal eosinophilia (peak density ≥15 eosinophils per high-power field) (Fig. 334-12). Complications of EoE in adolescents and adults include food impac tion, esophageal stricture, narrow-caliber esophagus, and (rarely) esophageal perforation. In children, complications include feeding difficulties and weight loss. Since the complications of EoE are a consequence of ongoing eosinophilic inflammation, preventing them is dependent on follow up endoscopy with biopsies to verify a selected therapy's effectiveness in controlling eosinophilic inflammation. Primary therapy often starts with a PPI, which is effective at improving eosinophilic inflammation in 30–50% of patients. Additional first-line therapies include elimina tion diets or swallowed topical glucocorticoids. Elemental formula diets devoid of allergenic protein are a highly effective therapy but are limited by palatability. Notably, allergy testing by means of either serum IgE or skin prick testing has demonstrated poor sensitivity and specificity in the identification of foods responsible for EoE in an individual patient. Empiric elimination of common food aller gies (milk, wheat, egg, soy, nuts, and seafood) followed by systematic PART 10 Disorders of the Gastrointestinal System A B C D FIGURE 334-11 Endoscopic features of (A) eosinophilic esophagitis (EoE), (B) Candida esophagitis, (C) giant ulcer associated with HIV, and (D) a Schatzki ring.

FIGURE 334-12 Histopathology of eosinophilic esophagitis (EoE) showing infiltration of the esophageal squamous epithelium with eosinophils. Additional features of basal cell hyperplasia and lamina propria fibrosis are present. Eosinophilic inflammation can also be seen with gastroesophageal reflux disease. reintroduction has been an effective diet therapy in both children and adults. The intent of the elimination diet approach is the identification and long-term avoidance of specific food trigger(s). Swallowed, topical glucocorticoids (e.g., fluticasone propionate or budesonide) are effec tive in 50–80% of patients. Systemic glucocorticoids are not generally recommended due to side effects and lack of proven benefit beyond that achieved with topical glucocorticoids. The first U.S. Food and Drug Administration–approved treatment for EoE is the interleukin 4 and 13–blocking biologic dupilumab, injected subcutaneously once a week. Additional therapies targeting other immune pathways and allergic cytokine mediators have also shown promise in initial clinical trials. Esophageal dilation is highly effective at relieving dysphagia in patients with fibrostenosis but does not address the underlying inflam matory process. Dilation should be approached cautiously because of the risk of deep, esophageal mural laceration or perforation in the characteristic stiff-walled esophagus. Once an effective therapy is identified, maintenance therapy is advocated due to the chronicity of EoE and nearly universal disease recurrence upon cessation of therapy. INFECTIOUS ESOPHAGITIS With the increased use of immunosuppression for organ transplanta tion and chronic inflammatory diseases, use of chemotherapy, and the AIDS epidemic, infections with Candida species, herpesvirus, and cytomegalovirus (CMV) have become relatively common. Although rare, infectious esophagitis also occurs among the non-immunocom promised, with herpes simplex and Candida albicans being the most common pathogens. Among AIDS patients, infectious esophagitis becomes more common as the CD4 count declines; cases are rare with a CD4 count >200 and common when <100. HIV itself may also be associated with a self-limited syndrome of acute esophageal ulceration with oral ulcers and a maculopapular skin rash at the time of sero conversion. Additionally, some patients with advanced disease have deep, persistent esophageal ulcers treated with oral glucocorticoids or

thalidomide. However, with the widespread use of highly effective anti viral therapies, these HIV complications have become less common. Regardless of the infectious agent, odynophagia is a characteristic symptom of infectious esophagitis; dysphagia, chest pain, and hem orrhage are also common. Odynophagia is uncommon with reflux esophagitis, so its presence should always raise suspicion of an alterna tive etiology. ■ ■CANDIDA ESOPHAGITIS Candida is normally found in the throat but can become pathogenic and produce esophagitis in a compromised host; C. albicans is most common. Candida esophagitis also occurs with esophageal stasis secondary to esophageal motor disorders and diverticula. Patients complain of odynophagia and dysphagia. If oral thrush is present, empirical therapy is appropriate, but co-infection is common, and per sistent symptoms should lead to prompt endoscopy with biopsy, which is the most useful diagnostic evaluation. Candida esophagitis has a characteristic appearance of white plaques or exudate with friability. Oral fluconazole (400 mg on the first day, followed by 200 mg daily) for 7–14 days is the preferred initial treatment. Patients refractory to that may respond to higher dose fluconazole, voriconazole, itraconazole, or posaconazole. Alternatively, poorly responsive patients or those who cannot swallow medications can be treated with an intravenous echi nocandin or amphotericin B. ■ ■HERPETIC ESOPHAGITIS Herpes simplex virus type 1 or 2 may cause esophagitis. Vesicles on the nose and lips may coexist and are suggestive of a herpetic etiology. Varicella-zoster virus can also cause esophagitis in children with chick enpox or adults with zoster. The characteristic endoscopic findings are vesicles and small, superficial ulcerations. Because herpes simplex infections are limited to squamous epithelium, biopsies from the ulcer margins are most likely to reveal the characteristic ground-glass nuclei, eosinophilic Cowdry’s type A inclusion bodies, and giant cells. Cul ture or polymerase chain reaction (PCR) assays are helpful to identify acyclovir-resistant strains. Acyclovir (200 mg orally five times a day for 7–10 days) can be used for immunocompetent hosts, although the dis ease is typically self-limited after a 1- to 2-week period in such patients. Immunocompromised patients are treated with acyclovir (400 mg orally five times a day for 14–21 days), famciclovir (500 mg orally three times a day), or valacyclovir (1 g orally three times a day). In patients with severe odynophagia, intravenous acyclovir, 5 mg/kg every 8 h for 7–14 days, reduces this morbidity. ■ ■CYTOMEGALOVIRUS CMV esophagitis occurs primarily in immunocompromised patients, particularly those with HIV, malignancy, and recipients of bone mar row or organ transplants. CMV is usually reactivated from a latent infection. Endoscopically, CMV lesions appear as large serpiginous ulcers in an otherwise normal mucosa, particularly in the distal esoph agus. Biopsies from the ulcer bases have the greatest diagnostic yield for finding the pathognomonic large nuclear or cytoplasmic inclusion bodies. Immunohistology with monoclonal antibodies to CMV and in situ hybridization tests are useful for early diagnosis. Data on therapy for CMV esophagitis are limited. Treatment studies of CMV gastroin testinal disease have demonstrated effectiveness of both ganciclovir (5 mg/kg every 12 h IV) and valganciclovir (900 mg orally every 12 h). Therapy is continued until healing, which may take 3–6 weeks. Mainte nance therapy may be needed for patients with relapsing disease. MECHANICAL TRAUMA AND

IATROGENIC INJURY ■ ■ESOPHAGEAL PERFORATION Most cases of esophageal perforation are from instrumentation of the esophagus or trauma. Alternatively, forceful vomiting or retch ing can lead to spontaneous rupture at the gastroesophageal junction (Boerhaave’s syndrome). More rarely, corrosive esophagitis or neo plasms lead to perforation. Instrument perforation from endoscopy

or nasogastric tube placement typically occurs in the hypopharynx or at the gastroesophageal junction. Perforation may also occur at the site of a stricture in the setting of endoscopic food disimpaction or therapeutic esophageal dilation. Esophageal perforation causes pleu ritic retrosternal pain often associated with pneumomediastinum and subcutaneous emphysema. Mediastinitis is a major complication of esophageal perforation, and prompt recognition is key to optimizing outcome. CT of the chest is most sensitive in detecting mediastinal air. Esophageal perforation is confirmed by a contrast swallow, usually Gastrografin followed by thin barium. Treatment includes nasogastric suction and parenteral broad-spectrum antibiotics with prompt surgi cal drainage and repair in noncontained leaks. Conservative therapy with nasogastric suction, NPO status, and antibiotics without surgery may be appropriate in cases of contained perforation that are detected early. Endoscopic clipping or stent placement may be indicated in nonoperated iatrogenic perforations or nonoperable cases such as perforated tumors.

■ ■MALLORY-WEISS TEAR Vomiting, retching, or vigorous coughing can cause a nontransmural tear at the gastroesophageal junction that is a common cause of upper gastrointestinal bleeding. Most patients present with hematemesis. Antecedent vomiting is the norm but not always evident. Bleeding usually abates spontaneously, but protracted bleeding may respond to local epinephrine or cauterization therapy, endoscopic clipping, or angiographic embolization. Surgery is rarely needed. ■ ■RADIATION ESOPHAGITIS Radiation esophagitis can complicate treatment for thoracic cancers, especially breast and lung cancers, with the risk proportional to radia tion dosage. Radiosensitizing drugs such as doxorubicin, bleomycin, cyclophosphamide, and cisplatin increase the risk. Dysphagia and odynophagia may last weeks to months after therapy. The esophageal mucosa becomes erythematous, edematous, and friable. Submucosal fibrosis and degenerative tissue changes and stricturing may occur years after the radiation exposure. Radiation exposure in excess of 5000 cGy has been associated with increased risk of esophageal stricture. Treatment for acute radiation esophagitis is supportive. Chronic stric tures are managed with esophageal dilation. CHAPTER 334 Diseases of the Esophagus ■ ■CORROSIVE ESOPHAGITIS Caustic esophageal injury from ingestion of alkali or, less commonly, acid can be accidental or from attempted suicide. Absence of oral injury does not exclude possible esophageal involvement. Thus, early endoscopic evaluation is recommended to assess and grade injury to the esophageal mucosa. Severe corrosive injury may lead to esopha geal perforation, bleeding, stricture, and death. Glucocorticoids have not been shown to improve the clinical outcome of acute corrosive esophagitis and are not recommended. Healing of more severe grades of caustic injury is commonly associated with severe stricture forma tion and often requires life-long repeated dilation. ■ ■PILL ESOPHAGITIS Pill-induced esophagitis occurs when a swallowed pill fails to traverse the entire esophagus and lodges within the lumen. Generally, this is attributed to poor “pill-taking habits”: inadequate liquid with the pill or lying down immediately after taking a pill. The most common location for the pill to lodge is in the mid-esophagus near the crossing of the aorta or carina. Extrinsic compression from these structures halts the movement of the pill or capsule. Since initially reported in 1970, thousands of cases of pill esophagitis have been reported, suggesting that this is not an unusual occurrence. A wide variety of medications are implicated, with the most common being doxycycline, tetracycline, quinidine, phenytoin, potassium chloride, ferrous sulfate, nonsteroidal anti-inflammatory drugs (NSAIDs), and bisphosphonates. Typical symptoms of pill esophagitis are the sudden onset of chest pain and odynophagia. Characteristically, the pain will develop over a period of hours or will awaken the individual from sleep. A classic history in the setting of ingestion of a recognized pill offender obviates

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