Introduction

The list of symptoms that strongly suggest the presence of an esophageal disorder is relatively small (Table 1.1). None of these typical symptoms are specific to a particular esophageal disorder. In addition, there are a variety of symptoms or signs that (1) are infrequent, atypical manifestations of esophageal disorders, (2) are more commonly seen with nonesophageal disorders, (3) represent extraesophageal complications of the underlying esophageal disorder, or (4) have an inconsistent or unproven relationship to esophageal disorders (Table 1.2). Symptoms may arise from disorders intrinsic to the esophagus or conditions that affect the esophagus secondarily.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is by far the most common esophageal disorder. Gastroesophageal reflux occurs in normal individuals, and there is some overlap in the amount of reflux seen in healthy subjects and those diagnosed with GERD. This overlap and the fact that otherwise healthy individuals may occasionally note some manifestations of reflux events are taken into account in the Montreal consensus definition of GERD as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.”

Benson T. Massey, MD, FACP and Reza Shaker, MD, MACP
**Pathophysiology of GERD**

The most common mechanism by which gastric contents reflux into the esophagus is the transient lower esophageal sphincter relaxation (TLESR). TLESRs are characterized by brief (<1 minute) inhibition of the tone of the lower esophageal sphincter (LES), cessation of the phasic respiratory contractions of the diaphragmatic crura, and reduction in the contractility of the circular muscle of the esophageal body.\(^2-4\) In addition, contraction of the esophageal longitudinal muscle during a TLESR can be strong enough to pull the gastroesophageal junction into the thoracic cavity.\(^5,6\) These actions allow movement of gastric contents from a region of higher intraluminal pressure in the abdomen to the lower intraluminal pressure of the thoracic esophagus. TLESRs may be accompanied by relaxation or contraction of the upper esophageal sphincter (UES).\(^7-9\) Relaxation of the UES in the presence of gas reflux can result in belching, whereas liquid refluxates may be regurgitated into the pharynx. Reflexive contractions of the UES will block orad movement of esophageal contents into the upper aerodigestive tract.

TLESRs require an intact vagal innervation. Neurotransmission between the afferent and efferent limbs of the TLESR response are mediated or modulated by nitric oxide as well as cholecystokinin A, gamma-aminobutyric acid B, and metabotropic glutamate receptors.\(^10-13\) TLESRs are triggered by distension of the stomach; are more common in the awake, postprandial state; and are reduced in frequency during recumbency and deep sleep.\(^2,14,15\) TLESRs are a normal physiologic process that facilitates the venting of swallowed air from the upper digestive tract. Some degree of liquid reflux occurs normally as part of this process.

TLESRs occur with similar frequency in healthy subjects and patients with GERD.\(^16\) Where patients with GERD differ from healthy subjects is in the nature of the reflux events that accompany TLESRs, with GERD patients developing more acid reflux during TLESRs and more proximal migration of refluxate into the esophageal lumen.\(^16,17\) While TLESRs are the dominant mechanism for reflux in patients with GERD, those who have lost tonic function of the LES or developed abnormalities in the normal valvular anatomy of the gastroesophageal junction exhibit additional processes for displacement of gastric contents into the esophageal lumen, including continuously low LES pressure, reflux during abdominal straining, and re-reflux of gastric contents.\(^3,17-20\) Pediatric patients show similar mechanisms for reflux.\(^21,22\) Hiatal hernia is a risk factor for the presence of erosive esophagitis in both adult and pediatric patients with GERD.\(^23-26\) Although ingested food buffers gastric acidity, an "acid pocket" can persist in the
proximal stomach post-prandially. This acid pocket extends above the diaphragm and even up into the distal esophagus, particularly in GERD patients with hiatal hernia. In this situation TLESR events are more likely to be accompanied by acid reflux.27

Conditions that increase the pressure differential between the abdominal and thoracic cavities or cause retention of gastric contents will promote reflux. Obese subjects, who have higher intra-abdominal pressures,28 have greater TLESR responses to gastric distension following a meal,29 more acid reflux events on ambulatory pH monitoring,30 and more proximal migration of refluxate into the esophagus.31 Conversely, in patients with lung disease, such as cystic fibrosis, the lower inspiratory thoracic pressure induces more proximal reflux.32 Some patients with GERD have delayed emptying of the proximal stomach.33 Consumption of high-fat meals, which empty more slowly from the stomach, are associated with GERD.34 Also, dietary patterns that result in increased colonic fermentation can increase TLESRs and symptomatic reflux.35

**Symptom Manifestation**

Clinical sequelae of reflux depend on the duration and distribution of esophageal exposure to the refluxate. Extension of the refluxate into the proximal esophagus is more likely to be symptomatic,36 and migration past the UES into the pharynx predisposes the patient to oral and upper airway injury from the refluxate. The duration of esophageal acid exposure recording during ambulatory pH monitoring correlates with the severity of esophagitis,37 and GERD patients with complicated reflux disease have significantly greater esophageal acid exposure times than those without these complications.38 The duration of acid exposure depends on the interplay between the factors previously discussed that promote acid reflux events and those factors serving to clear refluxed acid from the esophagus. Esophageal clearance of acid depends on intact motor function of the esophageal body, as the refluxed volume is cleared by primary or secondary peristalsis. Patients with severe peptic esophagitis have a high incidence of esophageal peristaltic dysfunction.39 Restoration of the normal intraluminal esophageal pH also requires neutralization of acid retained in the esophageal mucous layer by the bicarbonate in swallowed saliva.40 Esophageal acid exposure to the point of inducing heartburn stimulates saliva production (water brash). Conditions that impair salivary production predispose patients to reflux esophagitis. Nocturnal reflux during transient awakenings often leads to prolonged episodes of acid exposure because swallowing and salivation are inhibited following return to sleep.

The contents of the refluxate determine the severity of symptoms and esophageal mucosal injury. Only a minority of reflux events are symptomatically perceived. Reflux events producing a lower value of intraluminal esophageal pH are more likely to result in heartburn,40 and the healing of esophagitis by proton pump inhibitors (PPIs) is associated with a reduction in the number of acid reflux events which is greater than the reduction in the total number of reflux events.41 However, reflux events containing gas in the refluxate are more likely to be perceived.42 Exposure to bile acids and pancreatic enzymes induces esophageal mucosal injury in animal models,43 and the duration of esophageal exposure to the contents of duodenogastric reflux is higher in patients with erosive esophagitis and Barrett’s esophagus.44 Patients with GERD overall do not have abnormal levels of gastric acid secretion. However, patients with acid hypersecretory states such as Zollinger-Ellison Syndrome are at risk to develop reflux esophagitis.45

Patients infected with *Helicobacter pylori* (HP) have reduced risks for developing reflux esophagitis, Barrett’s esophagus, and esophageal adenocarcinoma, an effect that may in part be mediated through gastric mucosal atrophy and the associated reduction in acid secretion that result from long-standing infection.46 Men without HP infection actually show increasing gastric acid secretion with age.47 While the presence of HP infection is associated with an improved response to therapy for GERD,48,49 eradication of HP does not seem to induce reflux symptoms in otherwise healthy subjects50 or increase the dose of acid suppression therapy needed to control symptoms in patients with reflux esophagitis.51

Recent evidence suggests that the development of esophageal mucosal lesions in response to the
noxious component of refluxate is not simply a direct chemical injury to the mucosa. Animal studies indicate the initial response is induction of an inflammatory cascade, involving both neurogenically mediated inflammation and the recruitment of inflammatory cytokines. Injury to the esophageal mucosa results in dilated intracellular spaces and increased mucosal permeability. These changes in mucosal permeability are associated with reductions in esophageal intraluminal and mucosal electrical impedance.

The development of symptoms such as heartburn or chest pain requires activation of esophageal nociceptors, with transmission of afferent pain signals via spinal afferent pathways to brainstem and higher cortical centers. The receptive fields for esophageal sensation show considerable overlap among different thoracic dermatomes. This in part explains the difficulty in localizing esophageal symptoms. Moreover, spinal afferent neurons can receive input from multiple thoracic structures, making it difficult at a cortical level to discriminate between esophageal and, for example, cardiac sources for pain. Esophageal pain pathways may develop both peripheral and central sensitization, wherein prior exposure to noxious stimuli lowers the threshold for subsequent noxious stimuli to initiate symptoms, as well as induce hyperalgesia and allodynia in adjacent structures. Thus a major determinant of whether any specific acid reflux event induces symptoms is the cumulative acid exposure during preceding time periods.

The threshold for reflux events to produce symptoms is lowered by acute auditory stress, and the burden of chronic life stress events is a major predictor of the severity of ongoing reflux symptoms over longer time periods. Sleep deprivation lowers the threshold for esophageal acid exposure to cause symptoms; this effect is likely compounded by the fact that GERD has a great effect on the quality of sleep. On the other hand, loss of normal nociceptive pathways may predispose the esophagus to injury. Patients with Barrett’s esophagus have been shown to have reduced sensitivity to acid infusion and esophageal distension, and have reduced symptom responses to acid reflux.

### Epidemiology, Risk Factors, and Natural History

GERD is the most commonly diagnosed gastrointestinal disorder, accounting for nearly 9 million outpatient visits annually in the United States. GERD occurs among all age cohorts, from infancy to senescence. Typical reflux symptoms such as regurgitation occur in the majority of healthy infants, with the prevalence of such symptoms progressively decreasing over the first 1–2 years of life. GERD symptoms are present in <10% of young children and adolescents. However, among infants diagnosed with reflux esophagitis, mucosal lesions persist over 1 year, even if symptoms resolve. A substantial fraction of children diagnosed with GERD have persistence of reflux symptoms and esophagitis into adolescence and early adulthood.

The estimates on prevalence of GERD among adults vary among studies, depending on the criteria for ascertaining the diagnosis. Studies on the prevalence of typical symptoms as an indirect marker for the presence of GERD indicate that about half of adults report such symptoms at some time, and about a fifth have symptoms at least weekly. Findings from population-based endoscopic screening studies indicate a lower prevalence of esophagitis (12–16%) of whom about one-third report no reflux symptoms. GERD is present around the globe and the prevalence appears to be increasing over time. While symptoms of GERD are seen frequently in both genders and ethnic groups, lower rates of complicat-

### Table 1.3 Risk Factors Associated with GERD

- Obesity
- Hiatal hernia
- Smoking
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Chronic atrophic gastritis/Helicobacter pylori infection (inverse association)
- Aging
- Irritable bowel syndrome
- Anxiety/depression
- Family history of GERD
ed reflux disease are seen in women and Blacks. The prevalence of GERD symptoms and complicated disease tends to increase with age.

Epidemiologic studies have identified several risk factors associated with the presence of GERD. Obesity and presence of a hiatal hernia are the dominant anatomic findings associated with reflux symptoms and esophagitis in studies throughout the world. Both the presence of infection with HP and the subsequent development of chronic atrophic gastritis have been associated with a reduced risk for reflux esophagitis. Among lifestyle factors, smoking has the most consistently positive association with GERD, whereas the findings for alcohol, caffeine, and other dietary components show either inconsistent or no such associations. Among medications, non-steroidal anti-inflammatory agents and aspirin are associated with GERD symptoms, ulceration, and stricture formation. The rate of co-occurrence of GERD and irritable bowel syndrome in the community is more than would be expected by chance. Both anxiety and depression are risk factors for the presence of GERD symptoms. Factors associated with the development of new GERD symptoms over time include older age, female sex, lower educational status, gain in BMI, and smoking. Family and twin studies have indicated a familial risk for GERD. The interplay between common environmental and genetic risks is not currently completely understood, although a recent genome-wide screening of patients with GERD implicates mutations involving the regulation of the gene for type III collagen in the development of hiatal hernias in men and GERD in both sexes.

Longitudinal studies of patients with GERD in clinical care show that many either acquire or lose the finding of erosive esophagitis with time. Overall, the incidence of new GERD symptoms exceeds the rate of loss, resulting in a net increase in GERD prevalence of 30% over 11 years in one study. Follow-up endoscopy in patients with GERD with initially normal mucosa shows a low (1-5%) likelihood for interval development of Barrett’s esophagus, whereas patients with esophagitis at initial endoscopy have up to a 5-fold higher risk to develop Barrett’s esophagus after five years of follow-up.

GERD-Related Syndromes

The Montreal Classification of GERD syndromes (Figure 1.1) incorporates research showing that for many patients the manifestations are symptomatic only, without evidence for overt damage to the esophagus or extraesophageal structures. It also takes into account those patients who have complications of GERD without manifesting typical GERD symptoms. Finally, it acknowledges the potential for extraesophageal complications of GERD, based on the strength of evidence for association and causality.

Complications of GERD

Esophagitis and Ulceration

GERD-related mucosal erosions typically have their base on the squamocolumnar junction and extend proximally in a flame-shaped distribution, but can extend to involve nearly the entire esophageal mucosa. The Los Angeles classification of erosive esophagitis has been demonstrated to have good intra- and interobserver agreement. Validity of this classification scheme is demonstrated by the association of higher grades with more esophageal acid exposure, greater reflux symptom severity, less frequent complete healing of esophagitis on therapy, and greater frequency of symptom relapse after a course of therapy.

Table 1.4

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>One (or more) mucosal break, ≤5 mm long, that does not extend between the tops of two mucosal folds</td>
</tr>
<tr>
<td>B</td>
<td>One (or more) mucosal break, &gt;5 mm long, that does not extend between the tops of two mucosal folds</td>
</tr>
<tr>
<td>C</td>
<td>One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but that involves &lt;75% of the circumference</td>
</tr>
<tr>
<td>D</td>
<td>One (or more) mucosal break that involves at least 75% of the esophageal circumference</td>
</tr>
</tbody>
</table>
Esophageal ulcers are more severe mucosal breaks, completely through the esophageal mucosa. The major complication from peptic esophagitis is bleeding. About one-fifth of patients undergoing endoscopic evaluation for upper gastrointestinal hemorrhage are found to have erosive esophagitis. In certain patient groups, such as the elderly and those with developmental abnormalities and/or cognitive impairment, reflux esophagitis may be the most common cause for upper gastrointestinal hemorrhage. Reflux esophagitis is an etiology for iron deficiency anemia in all age groups. Peptic strictures usually have a distal location near the squamocolumnar junction and are commonly accompanied by other mucosal changes from peptic injury, such as erosions, ulcerations, and Barrett’s mucosa. For strictures separated by more than a few centimeters from the squamocolumnar junction and intervening normal mucosa, other etiologies for the stricture must be considered, including pill injury, neoplasia, and eosinophilic esophagitis. The diameter of the narrowest part of the stricture determines the risk for dysphagia, and nearly all patients having strictures <12 mm in diameter report difficulties with solid foods. The severity of esophagitis accompanying the stricture also determines the degree of reported dysphagia. Additional symptoms associated with strictures are hiccups and retching.

**Figure 1.1**
Montreal Classification of Syndromes Resulting from GERD

Barrett’s esophagus
Barrett’s esophagus is the term used for the replacement of the normal squamous epithelium lining the esophagus with a columnar epithelium characterized by intestinal metaplasia containing goblet cells. The presence of Barrett’s esophagus is suspected when the squamocolumnar junction is displaced proximal to the anatomic gastroesophageal junction. The suspected diagnosis requires pathologic confirmation from biopsies of the abnormal-appearing mucosa. Barrett’s mucosa may range in length from the appearance of an irregular z-line to nearly complete replacement of the entire squamous mucosa in the esophageal body. The Prague C & M criteria for assessing the extent of the esophageal lumen involvement by Barrett’s epithelium have shown good interobserver agreement (Figure 1.2).  

Barrett’s esophagus can be seen at any age, but becomes more prevalent with increasing age. Endoscopic screening studies of adult populations have suggested an overall prevalence of 1–2%, with about half of subjects so identified not reporting typical GERD symptoms.  

The risk factors associated with Barrett’s esophagus are similar to those for uncomplicated GERD, but severe erosive esophagitis is an additional risk factor, as are male sex and white race. As observed in patients with erosive esophagitis, hiatal hernia, reduced LES pressure, and esophageal peristaltic dysfunction are commonly present and contribute to the excess esophageal acid exposure. Reflux of duodenal contents into the esophagus is also common in patients with Barrett’s esophagus. The major clinical concern for patients with Barrett’s esophagus is their greater risk for developing adenocarcinoma of the esophagus. Screening and surveillance for adenocarcinoma are covered in Chapter 14, Gastrointestinal Cancer.

Extraesophageal Manifestations
Gastroesophageal reflux can affect structures above the esophagus, either through the direct exposure of these structures to the noxious effects of the refluxate or via the activation of vago-vagal reflexes. The conditions for which extraesophageal reflux has been implicated are listed in Table 1.5. Structures located above the esophagus are not normally exposed to any acid reflux and do not have mechanisms available for acid neutralization and clearance. Even brief episodes of relatively minor exposure to noxious refluxate could have major pathologic and symptomatic consequences. Extraesophageal symptoms are present in about a third of patients with GERD.

Several factors make it difficult to attribute any individual patient’s extraesophageal symptoms and findings to GERD. First, the association may not be one of cause-and-effect but reflect a high degree of co-occurrence of the two conditions by unclear mechanisms. Second, the patient’s symptoms and findings may just as plausibly result from another unrecognized disorder. For example, chronic cough could also result from unidentified reactive airways disease, bronchiectasis, allergic laryngitis, or sinus disease. Third, initial descriptions of the association of severe extra esophageal manifestations with severe

**Figure 1.2**
Prague Classification of Barrett’s Esophagus

**Table 1.5**
Extraesophageal Manifestations and Associations of GERD

- Asthma
- Aspiration pneumonitis/pulmonary fibrosis
- Laryngitis/vocal cord lesions
- Laryngeal cancer
- Chronic cough
- Dental erosions
- Sinusitis
- Otitis media
reflux disease have not consistently been replicated with milder forms of these conditions. For example, the initial descriptions of severe ulcerative laryngitis and tracheal stenosis were seen as complications in patients with severe reflux disease, and brought to clinical awareness the concept of pathologic laryngopharyngeal reflux. However, attempts to ascribe less severe laryngeal findings and symptoms have been hampered by poor intra- and inter-observer agreement on the presence of laryngoscopic findings that are attributable to reflux. Furthermore, the majority of patients with these milder laryngeal findings have no evidence for esophagitis or hiatal hernia. Finally, some degree of supra-esophageal reflux can be seen in normal subjects, as can the laryngoscopic findings attributed to reflux disease. The natural history of laryngeal symptoms in patients with GERD is that these tend to resolve with time, in a course independent of the severity of the underlying reflux disease or treatment.

**Therapy for GERD**

**Lifestyle Modifications**

Lifestyle modifications for GERD include avoidance triggers such as consuming large meals, eating shortly before sleeping, and consuming foods and beverages that predictably cause symptoms. Patients with nighttime symptoms should elevate the head of the bed. Patients should be cautioned regarding the hazards of obesity, smoking, and use of nonsteroidal drugs, and encouraged to modify these risk factors. While the currently available evidence to support these suggested lifestyle changes is limited, their lack of expense and additional benefits to health make them reasonable interventions. However, these will be inadequate by themselves for most patients with GERD.

**Medical Therapy**

The mainstay for medical treatment of GERD in the twenty-first century is proton pump inhibitor (PPI) therapy. Most patients with GERD respond adequately to a single daily PPI dose, taken before the first meal of the day. With dose escalation to twice daily before meals when needed, the vast majority of patients with erosive reflux disease will heal and their symptoms will resolve on PPI therapy. There is no evidence to support more frequent dosing. The different available PPI agents are similar in their efficacy, and in the United States, the choice of agent for any particular patient is increasingly driven by formulary decisions of the patient’s insurance plan. Maintenance therapy at the dose needed for healing has the highest chance of maintaining remission, but patients may be titrated down to the lowest daily dose that permits control of symptoms. Patients with nonerosive reflux disease (NERD) can use short-course therapy for symptom recurrence, rather than continuous daily PPI therapy. Many NERD patients can use long-term PPI therapy include increased risk for bone fractures, infections such as *Clostridium difficile*, vitamin B12 deficiency, and reduced efficacy of clopidogrel therapy; none of these concerns to date have been substantiated in a prospective, placebo-controlled trial.

For patients who have intolerance to or contraindications for PPI therapy, the histamine2-receptor antagonists and sucralfate have some demonstrated efficacy above placebo, although the benefits are less than for PPI therapy. Agents combining alginate with an antacid can reduce esophageal acid exposure in the post-prandial period. Metoclopramide is not recommended as a primary or adjunct therapy for GERD. The efficacy for currently available anti-secretory therapies is greater for symptoms of heartburn than for regurgitation, and many patients with GERD continue to report incomplete symptom control on PPI therapy. Risk factors for failure of typical symptoms to respond to PPI therapy include lack of esophagitis or obesity and the presence of functional dyspepsia or irritable bowel syndrome. Patients with lower acid exposure times on ambulatory reflux testing are also less likely to have symptom improvement on PPI therapy.

**Surgery**

Laparoscopic antireflux surgery also has efficacy similar to PPI therapy in long-term follow-up studies. For surgery, a somewhat higher improvement
in primary GERD symptoms is offset by more symptoms of dysphagia and gas-bloat. About half of patients undergoing surgery require surgical revision or medical therapy over time. These factors, plus the risk of postoperative complications and the small risk of operative mortality, indicate that surgery should be reserved for those patients whose GERD-related symptoms and complications cannot be controlled adequately by medical therapy. For patients with medically-complicated obesity that warrants bariatric surgery, Roux-en-Y gastric bypass can be an effective antireflux procedure. However, vertical-banded gastroplasty is associated with a high rate of postoperative GERD. A variety of endoscopic approaches to create an antireflux barrier have been developed. None to date have demonstrated convincing durable efficacy and are not currently recommended.

**Extraesophageal Syndromes**

Placebo-controlled trials of acid suppressive therapy have not found significant benefit in the findings and symptoms of reflux laryngitis or in the treatment of asthmatics without reflux symptoms, even if abnormal esophageal acid exposure is present. Anti-reflux surgery is very unlikely to be helpful for extra-esophageal symptoms in the patient without concomitant heartburn and excessive (>12%) esophageal acid exposure. When therapy controls the cardinal symptoms of GERD, but atypical symptoms persist, the patient should be investigated for the presence of other disorders that could cause the latter.

**Peptic Stricture**

Dilation of peptic strictures improves symptoms of dysphagia. However, there is no proven benefit of dilating subtle, asymptomatic strictures that are found incidentally. If dysphagia is the dominant symptom and the stricture diameter is <12 mm diameter, then initial treatment with dilation will produce immediate benefit. For more patent and less symptomatic strictures, the option exists for an initial trial of PPI therapy. Control of GERD with PPI therapy reduces the need for repeat stricture dilation. Yet, this therapy will need to be continued indefinitely. For newly diagnosed strictures, if there is concern about the peptic etiology, obtaining mucosal biopsy specimens is prudent; repeat biopsy should also be considered if a presumed peptic stricture fails to respond to intervention. Patients with strictures should be cautioned to avoid medications with a high risk for esophageal injury, such as non-steroidal anti-inflammatory drugs and bisphosphonates.

**Barrett’s Esophagus**

Therapy in patients with Barrett’s esophagus is to control the symptoms of GERD, since neither medical nor surgical treatment results in clinically meaningful regression of Barrett’s mucosa. The current consensus recommendation is to control symptoms, not normalize esophageal acid exposure. Ongoing PPI therapy may inhibit the development of dysplasia in Barrett’s esophagus. However, neither medical nor surgical treatment of GERD has yet been shown to reduce the incidence of adenocarcinoma in patients with Barrett’s esophagus. Techniques for endoscopic mucosal ablation are not currently recommended for Barrett’s mucosa without high-grade or low-grade dysplasia. Chemoprevention with agents such as COX-2 inhibitors, is not recommended solely to treat Barrett’s esophagus. Surveillance of Barrett’s esophagus and treatment of associated dysplasia and adenocarcinoma are reviewed in Chapter 14 on Gastrointestinal Cancer. Smoking cessation should be recommended to all patients with known Barrett’s esophagus.

### Table 1.6

<table>
<thead>
<tr>
<th>Conditions Associated with Esophageal Eosinophilia</th>
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<tbody>
<tr>
<td>GERD</td>
</tr>
<tr>
<td>EoE</td>
</tr>
<tr>
<td>Eosinophilic gastritis/gastroenteritis/enteritis</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Drug reactions</td>
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<tr>
<td>Hypereosinophilic syndrome</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
</tr>
<tr>
<td>Esophageal motor disorders</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
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</tbody>
</table>
Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a clinicopathologic disease characterized by symptoms resulting from esophageal dysfunction accompanied by pathologic evidence of a predominantly eosinophilic inflammatory response confined to the esophagus. By consensus, in untreated patients the accepted density of eosinophilic infiltration is 15/high-powered field. Other conditions can cause esophageal eosinophilia, and these need to be excluded (see Table 1.6) before a diagnosis of primary EoE can be established. The entity of proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) does not fit clearly into this diagnostic scheme. This entity may represent a constellation of conditions, including GERD, true EoE that responds to further reduction of normal levels of esophageal acid exposure (or anti-inflammatory effects of PPI therapy), or co-occurrence of GERD and EoE, where treatment of GERD secondarily improves the EoE. PPI-REE and EoE cannot be distinguished on the basis of clinical symptoms, endoscopic findings, or tissue markers of eosinophilic inflammation.

Pathophysiology

A genetic basis for the disorder was first suggested by a high concordance for the disease among family members. Genome-wide analysis has identified the gene for the cytokine thymic stromal lymphopoetin (TSLP), involved in TH2 cell determination, is a susceptibility locus for EoE, as is a variant in the TSLP receptor gene (located on the X-chromosome) for male patients. A variant in the filaggrin gene (associated with atopic dermatitis) is more prevalent in EoE. Variants in the TGFB gene appear to determine response to topical steroid therapy. The esophageal mucosa in EoE shows over-expression of eotaxin-3 and up-regulation of interleukin-13. The majority of pediatric and adult patients exhibit allergic responses to food and/or aeroallergens, and most patients have other atopic disorders. Taken together, these findings support the concept of EoE as an allergic disorder, driven by exposure to common allergens. Specific variants in the genetic control of the immune response to antigenic stimulation likely result in the characteristic inflammatory/fibrotic responses within the esophagus.

Epidemiology and Natural History

Epidemiologic studies suggest a population based prevalence of <1 per 1000, while among unselected adult pa-
tients undergoing clinical endoscopic evaluation, esophageal eosinophilia may be found in up to 6.5%. Studies of pathology databases suggest a true increase in the incidence and prevalence of EoE over the past few decades. In adults, the diagnosis is less frequently made in winter months. EoE is more prevalent in male and non-Hispanic white patients. EoE occurs in all age groups.

**Clinical Presentation and Evaluation**

The most common clinical presentation is solid food dysphagia, and EoE has become the most common diagnosis in young patients presenting with food impactions. Pediatric patients are more likely to present with recurrent vomiting or food intolerance, but other esophageal symptoms, such as heartburn and chest pain, may be seen in all age groups. Pediatric patients may fall off the normal growth curve. No constellation of symptoms is pathognomonic for EoE. Most patients will have a history of other atopic (asthma, eczema, allergic rhinitis, food allergy) conditions.

The characteristic endoscopic features (Figure 1.3) of EoE are listed in Table 1.7, but it is important to recognize that some patients may have a normal endoscopic appearance. The presence of eosinophilic inflammation within esophageal mucosal biopsy specimens is required to make the diagnosis (Figure 1.4) By current consensus, eosinophil counts of ≥15 per high-powered field (HPF) are needed for the diagnosis. Diagnostic eosinophil counts may not be present during seasons with low levels of aeroallergens in some patients. Biopsies obtained when patients are treated can produce false negative results. Additional pathologic findings include eosinophilic microabscesses, basal cell hyperplasia, elongation of dermal pegs, superficial layering of eosinophils, extracellular eosinophil granules, and subepithelial fibrosis. The pathologic changes of EoE can be seen throughout the esophagus, but are often patchy in distribution, requiring multiple biopsies from different levels of the esophagus for adequate diagnostic sensitivity.

EoE patients with comorbid atopic illnesses or history of food allergies should be evaluated by an allergist. However, routine allergy testing for food and aeroallergens is not otherwise recommended.

**Therapy for EoE**

The first therapy needed for many patients with EoE is removal of food impactions; flexible endoscopy is safe in this setting and allows diagnosis of the underlying condition.
Dilation of rings and strictures is safe and effective therapy for improving dysphagia, but the need for repeat dilations with time is common. The mucosa in untreated EoE can tear easily, and dilation can produce deep rents into the mucosa that cause chest pain and odynophagia severe enough to require brief hospitalization for pain control and hydration. If care is taken to avoid excessive dilation in any one treatment session, risk of perforation is < 1%.\textsuperscript{132} The passage of single large-caliber (54–60 French) bougies to treat a seemingly isolated distal ring in EoE can be hazardous because endoscopically unrecognized stenoses may coexist proximally; dilation with graduated balloon catheters may be safer in this instance. Dilation therapy does not alter the underlying inflammatory process.\textsuperscript{151}

Unless there is a dominant stricture that is likely driving dysphagia symptoms, the current trend in EoE management is to defer dilation until the response to dietary and/or medical therapy is known (See Table 1.8). PPI therapy is a reasonable first line medical therapy for patients with suspected EoE because (1) this may uncover a case of PPI-REE\textsuperscript{152} and (2) this can address concomitant GERD in patients with EoE. Topical corticosteroid therapy, such as fluticasone or budesonide, has been shown to eliminate the eosinophilic infiltrate and esophageal proliferative responses and inconsistently improve symptoms in both pediatric and adult patients.\textsuperscript{153-157} Chronic therapy carries some risk of (typically mild or asymptomatic) esophageal candidiasis. Montelukast at high doses may improve symptoms, but without resolution of the mucosal eosinophilic infiltrate.\textsuperscript{158} Cromolyn sodium has not been shown to be beneficial. In a limited trial the anti–interleukin-5 antibody mepolizumab was shown to reduce tissue eosinophil levels without significant symptom resolution.\textsuperscript{159} Elemental and elimination diets to reduce antigenic stimulation have been beneficial in children,\textsuperscript{160,161} while a six food elimination diet has been shown to improve symptoms and resolve eosinophilic inflammation in adults.\textsuperscript{161} In this as well as in a pediatric study,\textsuperscript{162,163} the results of food allergy (skin prick) testing have not been shown to be reliable in predicting the causative foods on rechallenge.

Cessation of therapy for EoE results in relapse of pathologic changes and symptoms,\textsuperscript{164} and the effect of therapy on the long-term need for stricture dilation frequency is unclear. Comorbid atopic conditions, such as allergic rhinitis and asthma, should also be treated.\textsuperscript{165}

### Table 1.8
**Medical and Dietary Therapies for Eosinophilic Esophagitis**

<table>
<thead>
<tr>
<th>Modality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton Pump Inhibitor 20-40 mg qd to bid</td>
<td>Consider as initial treatment to exclude PPI-REE. Use to treat coexistent GERD.</td>
</tr>
<tr>
<td>Systemic corticosteroids 2 mg/kg/d (60 mg/d maximum)</td>
<td>For severe symptoms; 4 week course, then taper off. Requires other therapy for maintenance.</td>
</tr>
<tr>
<td>Fluticasone 880-1760 mcg/d Budesonide 1-2 mg/d</td>
<td>Better esophageal coating with viscous liquid formulations. Resolution of eosinophilia &gt; symptom improvement. Risk for candida esophagitis</td>
</tr>
<tr>
<td>Elemental diet</td>
<td>Most effective therapy in pediatric population. Expensive. Poorly tolerated (most require feeding tube).</td>
</tr>
<tr>
<td>Six food elimination diet (wheat, milk, eggs, soy, peanuts/tree nuts, fish/shellfish)</td>
<td>Consultation with dietician to assure appropriate elimination/nutritional balance. May be able to re-introduce some foods.</td>
</tr>
<tr>
<td>Targeted elimination diet based on allergy test findings</td>
<td>Current testing poorly predicts response in adults. Lower response than elemental diet in children. Added cost of testing.</td>
</tr>
</tbody>
</table>
Other Intrinsic Structural Disorders of the Esophagus

Congenital Esophageal Stenosis, Atresia, and Tracheoesophageal Fistula

Abnormal embryonic development arising in the esophageal and tracheal anlagen can result in incomplete separation of the esophagus from the trachea and incomplete development of the esophagus. The resulting defects range in severity from esophageal stenosis to tracheoesophageal fistula to esophageal atresia. Most of these present in the perinatal period with feeding difficulties, vomiting, cough productive of feedings, and pneumonia. Patients with more subtle stenoses may not present with dysphagic symptoms until adulthood. The defects can often be bridged using a gastric tube reconstruction, but with the obligate absence of a lower esophageal sphincter and normal esophageal motility, these patients are at high risk for subsequent complications of GERD.

Inlet Patch (Gastric Heterotopia)

About 1–10% of individuals have an inlet patch of columnar mucosa located at or below the distal aspect of the UES; the detection rate is higher when endoscopic examination is focused on identifying these lesions and narrow-band imaging is employed. Whether the origins are congenital or develop secondarily is not clear, as reflux esophagitis and Barrett’s esophagus are common associated findings. Most inlet patches are asymptomatic, but some larger patches appear capable of secreting acid and may be complicated by symptoms of globus and dysphagia. Complications include esophageal strictures, ulcers, and rare neoplastic degeneration.

Esophageal Manifestations of Systemic Disorders

Many systemic conditions can affect the esophagus secondarily. In some cases, esophageal complications first bring the disorder to medical attention and can be the most problematic manifestation for some patients.

Diabetes

Several factors predispose diabetic patients to develop GERD and its complications. Importantly, the majority of patients with type 2 diabetes are obese. Additionally, hyperglycemia increases the rate of TLESR response to gastric distension in healthy subjects, and diabetic patients with higher glycosylated hemoglobin values are more likely report GERD symptoms. Many patients with diabetes have delayed gastric emptying, predisposing them to reflux. Patients with diabetes may also be less sensitive to the presence of abnormal amounts of reflux and thus may not come to clinical attention until they develop more severe complications of peptic esophagitis. Reflux esophagitis is the most common finding in patients with diabetic ketoacidosis and upper gastrointestinal hemorrhage. Diabetes is a risk factor for developing Candida esophagitis.

Connective Tissue Disorders

In patients with progressive systemic sclerosis or mixed connective tissue disease, the reduction in LES pressure and peristaltic function from atrophy of the smooth muscle predisposes these patients to severe reflux disease, as does the delayed gastric emptying that is also frequently present in these patients. Uncontrolled reflux may be a risk factor for chronic aspiration and pulmonary fibrosis in these patients. Patients with Sjögren’s (sicca) syndrome have reduced ability to neutralize refluxed acid. The loss of the lubricating properties of saliva also causes dysphagia for solids. Patients with connective tissue disorders are at risk for iatrogenic complications from immunosuppression (infectious esophagitis) or pill injury (nonsteroidal anti-inflammatory drugs and bisphosphonates for arthritis and osteoporosis).

Table 1.9

<table>
<thead>
<tr>
<th>Primary Dermatologic Disorders Affecting the Esophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Lichen planus</td>
</tr>
</tbody>
</table>

Chapter 1 — Esophageal Disorders
Dermatologic Disorders
Due to its squamous epithelium, the esophagus is subject to several systemic diseases typically affecting the skin (Table 1.9). These immune-mediated disorders can manifest on endoscopy as blisters, a positive Nikolsky’s sign, erosions, plaques, ulcers, and strictures. The presence of skin and oral lesions usually provides clues to the diagnosis, although esophageal involvement is rarely the presenting manifestation. Immuno-fluorescent staining of biopsy specimens can confirm the diagnosis.

Infection
The major clinical infections of the esophagus are Candida, herpes, and cytomegalovirus. The most common symptom of infectious esophagitis is odynophagia. Risk factors for all infections include profound suppression of the immune system, as can be seen in patients with acquired immunodeficiency syndrome or in patients on immunosuppressive therapy for transplants. Poorly controlled HIV infection itself can be associated with large ulcers that are negative for other infectious agents. Additional risk factors for fungal infections include diabetes, recent antibiotic exposure, and swallowed topical corticosteroid therapy. Candidal infections usually have an endoscopic appearance of a whitish exudate (“cottage cheese”), while viral infections typically cause esophageal ulceration.

Cardiovascular Disorders
The major clinical issue regarding cardiovascular disorders and the esophagus is the need to avoid ascribing symptoms from cardiac disease to the esophagus. While GERD may cause chest pain in patients with known coronary artery disease, the obverse is also true. Patients with coronary artery disease may present with vague chest symptoms ascribed to heartburn, or atypical gastrointestinal symptoms such as nausea or eructation, and there is some evidence in population studies that misdiagnosis of myocardial infarction as GERD is an important problem. Complicating matters further is that fact that GERD is a common comorbidity in patients with coronary artery disease, and esophageal acid exposure can reduce coronary blood flow via a vagal reflex.

Congenital or acquired abnormalities of the cardiovascular system can obstruct the esophagus via extrinsic compression (dysphagia lusoria). Dissection of the thoracic aortic may cause acute esophageal necrosis. Rupture of an aortic aneurysm into the esophagus is usually a fatal event, presenting as massive hematemesis.

Accidental and Latrogenic Esophageal Disorders

Esophageal Pill Injury, Caustic Ingestion, and Foreign Bodies
Well over 100 medications have been reported to cause pill-induced esophageal injury. The most common agents in clinical practice are listed in Table 1.10. Doxycycline is notorious for causing severe odynophagia, but this symptom is seen with many other agents, as well as symptoms of heartburn, chest pain, and dysphagia. Injury can range from erosions to deep ulcers to perforation, and the initial lesion may evolve into a refractory stricture. A clue to the etiology of these lesions is their common locations above the level of the lower esophageal sphincter and above the aortic arch, unlike lesions from GERD, which are usually based on or just above the squamocolumnar junction. A common history preceding such injury is that the patient swallowed the pill dry and/or while recumbent. Risk factors for pill injury are old age and sustained release preparations.

Table 1.10
Common Medications for Pill-Induced Esophageal Injury

- Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)
- Bisphosphonates
- Potassium chloride
- Doxycycline/tetracycline
- Ascorbic acid
- Ferrous sulfate
Extremely acid (pH <2) or alkaline (pH >12) solutions can cause severe esophageal injury. A full thickness injury may result in perforation acutely and chronic stricture formation, requiring repeated courses of dilation. Some patients will require esophageal replacement. Early endoscopy (within 24 hours) is safe and warranted to assess the severity of injury in patients who have symptoms after reported ingestion. A lack of oral lesions does not exclude severe injury more distally in the esophagus.

Inadvertent or intentional ingestion of sharp or pointed foreign bodies, such as bones, pins, and razor blades, places the patient at risk for esophageal laceration or perforation, with subsequent development of mediastinitis or fistula into the cardiovascular system. Retained button batteries can produce a deep tissue injury. Retained esophageal foreign bodies constitute an endoscopic emergency.

**Medication and Radiation Effects**

Medications that inhibit smooth-muscle tone or contractility can theoretically place patients at higher risk for gastroesophageal reflux and delayed clearance of refluxate. Such agents include calcium channel blockers, theophylline, and beta-agonists, the latter two being used frequently in asthmatics, who commonly have coexisting GERD. Agents with anticholinergic properties can also decrease salivary secretion, resulting in impaired neutralization of refluxed acid.

Ionizing radiation has both early and delayed effects on the esophagus. Acutely, the inflammatory response may cause dysphagia and odynophagia severe enough to require alternate means of alimentation. More severe injury can lead to extensive transmural necrosis, with hemorrhage and perforation. Later effects tend to be from stenosis, which may extend to complete luminal occlusion. Concurrent chemotherapy increases the risk of injury for any given course of radiation therapy. Patients with radiation-induced xerostomia have a higher frequency of abnormal esophageal acid exposure and reflux esophagitis.  

**Consequences of Instrumental and Surgical Procedures**

Passage of instrumentation into the esophageal lumen carries a small risk of abrasion, laceration, hematoma, or frank perforation of the esophagus. This risk becomes much greater in the presence of structural disorders, such as rings and strictures, particularly since subtle strictures may not be easily recognized at the time of endoscopy. Perforation is the dreaded complication of stricture dilation; the time-honored dictum is to pass no more than three successively larger dilators, once resistance to dilator passage is present, in any one session. Treatments to eradicate abnormal mucosa and vessels in the esophagus may produce strictures.

Immediate iatrogenic injuries from esophageal surgery include mucosal tears, frank perforations, intramural hematomas, ischemic necrosis, and anastomotic strictures and leaks. Patients undergoing antireflux surgery may have immediate or delayed symptoms from overly tight or long wraps, slipped wraps, or development of a paraesophageal hernia. About half of patients following a myotomy for achalasia develop symptoms or findings of GERD.

Patients undergoing radiofrequency ablation for cardiac arrhythmias are at risk to develop thermal injury to the adjacent esophagus. Such lesions are not always symptomatic, but the concern is for the rare development of fatal cardioesophageal fistula formation following such transmural esophageal injury.

**Motor, Neoplastic, and Portal Hypertensive Disorders of the Esophagus**

These topics are covered in separate chapters. The clinician must remain aware that these can coexist with other esophageal disorders. For example, patients with esophageal achalasia may suffer from pill injury, Candida esophagitis, reflux disease (following surgical myotomy), or esophageal cancer. Patients with GERD and Barrett’s esophagus may develop adenocarcinoma of the esophagus. Patients may develop esophageal strictures from efforts to eradicate varices. Patients with motor disorders can develop Zenker’s and other pulsion diverticula.
Figure 1.5
Flow Charts for the Evaluation of the Patient with Symptoms Suggesting the Presence of an Esophageal Disorder.

Figure 1.5 shows the initial approach to a suspected esophageal disorder, depending on the nature of the presenting symptoms and the additional work-up to perform if the patient fails to respond to a PPI trial and/or EGD testing is nondiagnostic. DX, diagnosis made; CAD, coronary artery disease; PPI, proton pump inhibitor therapy; EGD, upper endoscopy.
Chapter 1 — Esophageal Disorders

Approach to the Patient with Suspected Esophageal Disorders

The patient history remains the cornerstone of evaluation when esophageal disorders are suspected, with emphasis on the presence, severity, time course, and associations of cardinal and atypical symptoms. History-taking should also address the presence of conditions that secondarily affect the esophagus, as should the physical examination (which is typically normal for primary esophageal disorders). Additional testing is usually necessary to obtain an accurate diagnosis of esophageal disorders, with the sequence of testing being guided by findings from the history and physical examination findings in conjunction with knowledge regarding the background prevalence and clinical associations of the different esophageal disorders.

Diagnostic Strategies and Options for Testing

Rational and cost-effective testing and treatment in the twenty-first century are based on the knowledge that the most prevalent esophageal disorder by far is GERD. Even patients presenting with atypical symptoms are more likely to have GERD than another esophageal disorder. This high prior probability of GERD drives the diagnostic algorithm outlined in Figure 1.5.

For patients presenting with the classical symptoms of heartburn (typically postprandial substernal burning with upward radiation) and sour regurgitation, the likelihood that they have GERD as the etiology is so great that a trial of PPI therapy can be both diagnostic and therapeutic. If the patient responds appropriately, no other testing is necessary to confirm the diagnosis. The utility of evaluating such patients for asymptomatic complications of GERD, such as Barrett’s esophagus, is controversial. Any such testing should be guided by the presence of known risk factors for Barrett’s esophagus.

On the other hand, patients who have other cardinal symptoms, such as odynophagia and troublesome dysphagia (not mild, brief, and infrequent bolus hesitancy or sticking sensations) should undergo early endoscopic evaluation, because of the greater likelihood of GERD complications or the presence of another serious esophageal disorder. Endoscopic evaluation of dysphagia should include random biopsies from the proximal and distal esophagus (if no other explanation for dysphagia is seen), to identify otherwise unsuspected EoE. Early endoscopy should also be performed in patients with additional alarm symptoms, such as weight loss, failure to thrive, repetitive vomiting, or hematemesis. Patients with a combination of cardinal and atypical symptoms are also candidates for early endoscopy, as are patients over age 55 with dyspeptic symptoms.

Careful consideration has to be given to the patient presenting only with chest discomfort atypical for GERD. The concern is that the patient has undiagnosed coronary artery disease (CAD). CAD and GERD share many of the same risk factors and commonly occur together. Such patients warrant rigorous evaluation to exclude a cardiac source of pain before evaluation of possible esophageal sources. For patients with these atypical coronary syndromes, resting EKG and routine exercise stress testing alone may not be adequately sensitive.

Following a negative cardiac evaluation for patients with only chest pain, and a negative endoscopy in patients with other cardinal esophageal symptoms, the next reasonable step is a diagnostic/therapeutic trial of PPI therapy (once daily, followed by twice daily if no response, each for at least 8 weeks), since in this setting the most likely remaining diagnosis is still GERD. Patients who fail a PPI trial should proceed to endoscopy, if this has not already been done, as the chances for finding other esophageal disorders or complications of GERD on such testing become greater in this setting.

After a negative endoscopy, if the patient’s dominant symptom is solid food dysphagia, the next test should be a barium pharyngoesophagram that incorporates a solid bolus challenge, to assess for previously missed subtle rings, webs, and stenoses. Otherwise (and if the esophagram is negative), the next test should be an esophageal manometry to detect the presence of an esophageal motor disorder, such as achalasia or distal esophageal spasm.

At this point, the patient in whom preceding testing was non-diagnostic and whose cardinal symp-
Symptoms failed to respond to a PPI trial should undergo ambulatory esophageal pH testing. This can be combined with impedance for assessing nonacid reflux, to determine whether the patient may have nonerosive reflux disease (NERD) that failed to respond to therapy and is temporally associated with the patient’s symptoms. The preceding manometric evaluation will also aid in probe placement. Ambulatory reflux testing should be performed off of therapy, since the goal at this point is to confirm that GERD is indeed present. For patients with GERD documented previously but poor response to therapy, a case can be made for ambulatory reflux testing on twice daily PPI therapy to document failure of such therapy, but with an expected yield of less than one in ten.

In patients whose diagnostic evaluation remains inconclusive after the above sequence, the most likely etiology for symptoms is a sensory disturbance, such as functional heartburn, which may not necessarily have its origin in the esophagus. Alternatively, the chances are greater at this point that the symptoms come from a nonesophageal disorder. Finally, a careful review of prior testing should be undertaken, to assess for test quality concerns and other reasons for false-negative testing.

For some patients without cardinal esophageal symptoms, the issue is whether their atypical symptoms might be from an esophageal disorder. In these cases, the prior probability of an underlying esophageal disorder is so low that the patient would be best served by evaluation first for other disorders that are more likely to be the source of symptoms. Once other causes are excluded, evaluation can proceed along the lines described for patients with cardinal esophageal symptoms, with the proviso that patients with candidate supraesophageal symptoms are unlikely to respond to PPI trials when typical GERD symptoms are absent.

Unfortunately, a common clinical scenario is the patient whose test results support the diagnosis of GERD but who fails to respond to GERD-directed therapy. The most plausible reasons for this failure are in Table 1.1. Compliance has become a greater issue, as expensive PPI agents have become available over the counter and are no longer covered by insurance. Patients are often not instructed as to the appropriate timing of PPI therapy, which should be taken before meals. Unrecognized conditions that could be impairing the response to therapy at this point include celiac disease, surreptitious nonsteroidal anti-inflammatory drug (NSAID) use/abuse, and systemic sclerosis. The most common causes for false-positive endoscopic diagnoses of GERD are erosions from pill injury and strictures from EoE. Repeat ambulatory pH/impedance testing should be performed on therapy in this setting, as it may help identify those patients whose therapy is not controlling their reflux.

For the patient who fails to respond to antireflux surgery, or relapses after initial success, endoscopy is the first test, the goal being to assess integrity of the surgical repair and such complications as the development of a paraesophageal hernia. Endoscopy can also detect whether the patient has a new, or previously missed, esophageal disorder. If endoscopy is unrevealing, the next test should be esophageal manometry, especially if this was not performed preoperatively. If these tests are negative and the patient fails a PPI test, ambulatory pH monitoring is likely to be normal. Such patients are likely to have functional disorders as the cause of their symptoms.

The capabilities and caveats for the major tests to evaluate esophageal disorders are described below. The lack of perfect sensitivity and specificity of these tests must be considered when they are used to evaluate patients with a low pretest likelihood of an esophageal disorder, such as those with only atypical symptoms. In this setting, negative test results are often the most helpful, because the post-test probability is sufficiently low that esophageal etiologies can be removed from further consideration.

**Proton Pump Inhibitor Test**

The virtue of the PPI test for GERD, which is simply assessing whether the patient’s symptoms respond to a short course of PPI therapy, is its simplicity and low expense. However, the specific agent, dosage, and duration are not standardized, and a meta-analysis of trials of the PPI test indicate a sensitivity of 78% but a specificity of only 54%. Thus the test is useful only in cases where the pretest probability of GERD
is already large (typical GERD symptoms only, or prior testing excludes other candidate disorders). The recent recognition of the entity of PPI-responsive esophageal eosinophilia has further complicated the interpretation of the PPI test. An additional concern regarding the PPI test is the risk of development of symptoms from rebound acid hypersecretion upon PPI withdrawal.185

Endoscopy
Endoscopy allows the visual identification of mucosal and structural abnormalities in the esophagus and affords the opportunity to obtain diagnostic mucosal biopsies. Treatment of some disorders (stricture dilation, control of bleeding) can also be performed at the time of testing. False-positive results from endoscopy are usually related to misinterpretation of identified lesions (mistaking white spots of EoE for candidiasis, or ulcers from viruses or pill injury for GERD, or EoE strictures for peptic strictures). Preventable causes for false-negative endoscopies include failure to (1) examine the esophageal inlet carefully for webs and inlet patches, (2) recognize the characteristic features of EoE, (3) obtain mucosal biopsy specimens to diagnose EoE and (4) recognize abnormal post-operative anatomy.186 However, despite careful technique, subtle webs and stenoses may remain undetected. In addition, nearly half of patients with GERD do not have detectable endoscopic abnormalities, especially in an era when many patients are already on a PPI at the time of endoscopy.

Radiology
Barium fluoroscopic studies are insensitive to flat mucosal lesions, and the findings of reflux events during these studies do not reliably predict the presence of GERD.187 These studies can be useful for identifying subtle webs, rings, and stenoses that are not detectable by endoscopy, but this requires the additional use of an adequate-sized solid bolus challenge. Barium studies can also assess the detail of strictures too tight to allow endoscope passage and identify esophageal fistulas. Computed tomography (CT) imaging can detect pathologic thickening of the esophageal wall and extrinsic pathologic processes that compress or invade the esophagus.

Manometry
Manometry has no role in the diagnosis of GERD. Manometry is used to diagnose symptomatic major esophageal motor disorders and to exclude their presence in patients proposed for antireflux surgery. Manometry may be helpful in identifying symptomatically tight fundoplication wraps when endoscopic and radiologic testing is inconclusive. Manometry is also used for locating the position of the LES for placement of pH probes.

pH/impedance monitoring
Ambulatory pH monitoring allows the quantification of the degree of esophageal acid exposure and the correlation of symptoms with reflux events. A major problem with such testing is that no cutoff value for acid exposure completely separates normal subjects from those with GERD. The accuracy of pH testing

<table>
<thead>
<tr>
<th>No.</th>
<th>Reason for Therapeutic Failure in Patients Diagnosed with GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Noncompliance</td>
</tr>
<tr>
<td>2</td>
<td>Improper timing</td>
</tr>
<tr>
<td>3</td>
<td>Inadequate dosage</td>
</tr>
<tr>
<td>4</td>
<td>Inadequate delivery/bioavailability</td>
</tr>
<tr>
<td>5</td>
<td>Rapid medication metabolizer; true PPI resistance</td>
</tr>
<tr>
<td>6</td>
<td>Nocturnal acid breakthrough</td>
</tr>
<tr>
<td>7</td>
<td>Nonacid/weakly acid/duodenogastric reflux</td>
</tr>
<tr>
<td>8</td>
<td>Patient does not have GERD (prior test false-positive)</td>
</tr>
<tr>
<td>9</td>
<td>Patient has another esophageal disorder (e.g., achalasia, EoE)</td>
</tr>
<tr>
<td>10</td>
<td>Patient has a functional disorder (functional heartburn, hypersensitive esophagus, rumination)</td>
</tr>
<tr>
<td>11</td>
<td>Patient has a nonesophageal disorder (cardiac disease, asthma)</td>
</tr>
<tr>
<td>12</td>
<td>Patient has GERD plus another disorder</td>
</tr>
<tr>
<td>13</td>
<td>Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>14</td>
<td>EoE</td>
</tr>
<tr>
<td>15</td>
<td>Connective tissue disease (e.g., scleroderma)</td>
</tr>
<tr>
<td>16</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>17</td>
<td>Medication injury</td>
</tr>
<tr>
<td>18</td>
<td>Infection</td>
</tr>
<tr>
<td>19</td>
<td>Delayed gastric emptying</td>
</tr>
<tr>
<td>20</td>
<td>Functional gastrointestinal disorder</td>
</tr>
</tbody>
</table>
is at best about 90% in patients with GERD. Test-
ing can be performed with either catheter-based or
mucosally-attached sensors. The latter have the ad-
vantage of better tolerability by the patient and lon-
ger recording times; disadvantages include the cost
of a second endoscopy often used to place the probe
(and occasionally a third to remove probes causing
intolerable pain), and premature dislodgement and
migration of the sensor distally. This latter event can
give the false appearance of prolonged esophageal
acid exposure time. Distal single-site pH sensors are
unable to provide any information about the prox-
imal distribution of reflux events, which is a determi-
nant of symptom occurrence.

Probes are also available that record intralumi-
nal pH and impedance changes, the latter being used
to detect nonacid reflux events. Impedance can also
be used to prevent mistaking undocumented inges-
tion of acid foods as reflux events, which is a problem
for single-point pH sensors.

Ambulatory studies can be performed off or on
acid suppressive therapy, depending on whether the
goal is to help make the initial diagnosis of GERD or
to try to determine if persistent symptoms while on
therapy result from GERD that is not adequately treat-
ed under the current regimen. These studies can also
assess the temporal association of the patient’s symp-
toms with preceding acid or nonacid reflux events.
Limitations are failure to have a symptom event re-
ported during the recording period. Symptom asso-
ciations on studies with few events are unreliable.
For cough, it is often not possible to distinguish be-
tween coughs caused by reflux events or vice versa.

Illustrative Clinical Case

A 53-year-old woman presents with a 3-month histo-
ry of worsening heartburn and a 1-month history of
persistent dysphagia for breads and meats. She has
had occasional heartburn for years that she treated
with over-the-counter antacids. However, she has
been having more heartburn in the evening and
night, and started taking an over-the-counter his-
tamine2-receptor antagonists at bedtime last month
without much improvement. Her medical history is
pertinent for asthma, hypertension, hyperlipidemia,
obesity, and degenerative joint disease. Her other
medications are albuterol and fluticasone inhalers,
simvastatin, enalapril, and over-the-counter ibupro-
fen. Physical examination shows a blood pressure
(BP) of 134/80 mmHg and a body mass index (BMI)
of 32 kg/m², but is otherwise unremarkable.

Because of the new-onset solid-food dysphagia,
she undergoes an upper endoscopy, with findings
of Los Angeles Grade B erosive esophagitis at the
gastroesophageal junction, a 13-mm diameter ring-
type stricture at the gastroesophageal junction, and
a 2-cm fixed hiatal hernia. The ring is disrupted with
a 16-mm diameter balloon dilator, and the patient is
switched to a PPI before breakfast and advised to use
acetaminophen instead of ibuprofen for joint pain. On
follow-up one month later, dysphagia has resolved,
but she is having heartburn 3 nights per week.
Addition of a second dose of PPI before the evening
meal results in essentially complete resolution of her
symptoms after 2 additional months.

She does well until 2 years later, when she
develops burning substernal pain that can last for
hours and can awaken her, even though she continues
on her reflux medication. She intermittently notices
pain when swallowing her pills. Interval history is of a
new diagnosis of osteoporosis, which is being treated
with alendronate. She undergoes repeat endoscopy,
showing erosions at 25 cm from the incisors and at
4 cm above the gastroesophageal junction. Biopsies
are negative for EoE or infection, and she is advised
to discontinue the alendronate, with resolution of
her symptoms over the next week.

She again does well until 2 years later, when she
develops substernal chest discomfort at mealtime
or when walking her dog. An associated symptom is
nausea, and additional over-the-counter antacid
tablets do not help. Examination is unchanged except
for BMI of 34 kg/m² and BP of 148/92 mmHg. She is
referred to a cardiologist who performs a coronary
angiogram, showing a 90% occlusion in the right
coronary artery. A drug eluting stent is placed, and
she is begun on clopidogrel and low-dose aspirin,
with resolution of these symptoms.

This case illustrates several important concepts
in the evaluation and management of esophageal
disorders. The patient had several risk factors for her primary esophageal disorder of GERD. She had symptoms that should prompt endoscopic evaluation (and treatment). She required medication adjustments to provide adequate symptom relief. While her condition is a chronic one, she required careful reevaluation when she later experienced new symptoms while on effective therapy, due to the subsequent development of a new esophageal disorder and coronary artery disease.

**Pearls and Pitfalls for the Board Exam**
- Beware of “white spots” in the esophagus: these could be from Candida or EoE!
- Be able to recognize reflux events on pH/impedance tracings.
- No treatment is approved or has consensus recommendation for cancer prevention in Barrett’s esophagus without dysplasia.
- Recall the criteria for diagnosis of EoE, as well as the differential diagnosis of esophageal eosinophilia.
- Identify the different treatment options for EoE, including the condition of PPI responsive esophageal eosinophilia.
- Understand the concept of TLESR, but recognize that the presence of these by themselves do not distinguish GERD patients from healthy people.
- Be familiar with the appropriate dosage, timing, and duration of PPI administration.
- Watch out for the dysphagia patient with a “negative” EGD in which no biopsies were taken. What could have been missed: EoE, subtle ring/stricture, major motor disorder.
- Be aware of what normal and abnormal post-fundoplication anatomy looks like on EGD.
- Esophageal ulcers distant from the z-line? Think bugs and drugs (pill injury).
- Upper abdomen or chest discomfort not responding to PPI? Don’t forget the heart!

**References**

13. Frisby CL, Mattsson JP, Jensen JM, et al. Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate...
22


43. Tack J. Review article: role of pepsin and bile in gastro-


Chapter 1 — Esophageal Disorders


