Chapter 50: Gastroesophageal Reflux Disease

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 24, Gastroesophageal Reflux Disease.

KEY CONCEPTS

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1. Gastroesophageal reflux disease (GERD) can be described on the basis of either esophageal symptoms or esophageal tissue injury. The common symptoms include heartburn, regurgitation, chest pain, and dysphagia.

2. Endoscopy is commonly used to evaluate mucosal injury from GERD and to assess for the presence of Barrett's esophagus or other complications, such as strictures or adenocarcinoma.

3. Whereas ambulatory reflux monitoring only measures acid reflux, combined impedance–pH monitoring measures both acid and nonacid reflux.

4. The goals of GERD treatment are to alleviate symptoms and improve health-related quality of life, decrease the frequency of recurrent disease, promote healing of mucosal injury, and prevent complications.

5. GERD treatment is determined by disease severity and includes: (a) lifestyle changes and patient-directed therapy with antacids, nonprescription H2-receptor antagonists (H2RAs), and/or nonprescription proton pump inhibitors; (b) pharmacologic treatment with prescription-strength acid suppression therapy; (c) surgery; and (d) endoscopic therapies.

6. Patients with typical GERD symptoms should be treated with lifestyle modifications as appropriate and a trial of empiric acid suppression therapy. Those who do not respond to empiric therapy or who present with alarm symptoms such as dysphagia, weight loss, or gastrointestinal (GI) bleeding should undergo endoscopy.

7. Surgical intervention is a viable alternative treatment for select patients when long-term pharmacologic management is undesirable or when patients have complications.

8. Acid suppression is the mainstay of GERD treatment. Proton pump inhibitors provide the greatest symptom relief and the highest healing rates, especially for patients with erosive disease or moderate-to-severe symptoms or with complications.

9. Many patients with GERD will relapse if medication is withdrawn; so, long-term maintenance treatment may be required. A proton pump inhibitor is the drug of choice for maintenance of patients with moderate-to-severe GERD, erosive disease, or other complications such as Barrett's esophagus.

10. Patient medication profiles should be reviewed for drugs that may aggravate GERD. Patients should be monitored for adverse drug reactions and potential drug–drug interactions. Deprescribing PPIs or tapering to the lowest effective dose is a key strategy in preventing adverse effects.

BEYOND THE BOOK

BEYOND THE BOOK

Watch video entitled, "GERD" in AccessPharmacy. This ~6-minute video summarizes the normal function of the esophagus and stomach compared to that seen with acid reflux, complications of GERD, process of acid production, and pharmacologic therapy for GERD. Students' understanding regarding the Collect, Assess, and Plan steps of the Patient Care Process are addressed with this video.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common medical disorder.[1] GERD has been described based on its physiological, functional, and symptomatic attributes.[2,3] The Lyon consensus highlighted the physiological attributes of GERD, such as esophageal motor dysfunction and esophageal permeability issues. However, these abnormalities are nonspecific for GERD. The Rome IV conference described the functional syndromes with GERD characteristics. However, reflux causality cannot be made based on clinical presentation mimicking GERD.[2] The Montreal consensus defines GERD as "symptoms or complications resulting from refluxed stomach contents into the esophagus or beyond, into the oral cavity (including the larynx) or lung."[1] The key is that these troublesome symptoms, defined as symptoms occurring twice weekly or more, is that they adversely affect the well-being of the patient.[4] Episodic heartburn that is not frequent enough or painful enough to be considered bothersome by the patient is not included in this definition of GERD.

GERD can be further classified as either symptom-based or tissue injury–based depending on how the patient presents.[1] Symptom-based GERD may exist with or without esophageal injury, and most commonly presents as heartburn, regurgitation, or dysphagia (difficulty swallowing). Less commonly, odynophagia (painful swallowing), water brash, belching, bloating, or hypersalivation may also occur. The absence of tissue injury or erosions is commonly termed nonerosive reflux disease (NERD). The presence of abnormal acid exposure on ambulatory reflux monitoring differentiates NERD from functional heartburn where no abnormalities are seen.[5] NERD should also be differentiated from reflux hypersensitivity where patients have physiologic (normal) acid production but are symptomatic. Functional heartburn or reflux hypersensitivity may not respond well to acid suppression therapy since the underlying cause is not acid related.

Tissue injury-based GERD may exist with or without symptoms. The spectrum of injury includes esophagitis (inflammation of the lining of the esophagus), Barrett's esophagus (when tissue lining the esophagus is replaced by tissue similar to the lining of the intestine), esophageal strictures, and esophageal adenocarcinoma.[1] Esophagitis occurs when the esophagus is repeatedly exposed to refluxed gastric contents for prolonged periods of time.[1] This can progress to erosion of the squamous epithelium of the esophagus (erosive esophagitis). Esophagitis is classified as low grade (grade A or B) or high grade (grade C or D) based on the Los Angeles classification system. Complications of long-term reflux may include the development of esophageal strictures, Barrett's esophagus, or possibly adenocarcinoma of the esophagus.

Gastroesophageal reflux symptoms associated with disease processes in organs other than the esophagus are referred to as extraesophageal reflux syndromes. Patients with extraesophageal reflux syndromes may present with chest pain, hoarseness, chronic cough, or asthma. An association between these syndromes and GERD should only be considered when they occur along with esophageal GERD syndrome because these extraesophageal symptoms are nonspecific and have many other causes.[1]

Many patients suffering from mild GERD do not go on to develop erosive esophagitis and are often managed with lifestyle changes, antacids, and nonprescription histamine-2 receptor antagonists (H2RAs) or nonprescription proton pump inhibitors (PPIs). Those with more severe symptoms (with or without tissue injury) predictably follow a course of relapsing disease, requiring more intensive treatment with acid suppression therapy followed by long-term maintenance therapy. Periodic assessment is important to assure the lowest effective medication dose is being used. Antireflux surgery offers an alternative for select patients in whom prolonged medical management is undesirable, those with refractory GERD, or those with complications. Bariatric surgery may be an option in obese patients. Endoscopic therapies continue to be evaluated in an effort to find a less invasive alternative therapy that bridges the gap between pharmacologic management and more invasive surgery.

EPIDEMIOLOGY

GERD occurs most commonly in those older than 50 years of age.[6] Although mortality is rare, GERD may have a significant economic impact and decrease the quality of life. The true prevalence of GERD is difficult to assess because many patients do not seek medical treatment, symptoms do not always correlate well with the severity of the disease, and there is no standardized definition or universal gold standard method for diagnosing the disease. However, the

prevalence has risen significantly over the last 20 years with approximately 20% of adults in the United States suffering from GERD symptoms on a weekly basis.[7-9] The prevalence of GERD varies depending on the geographic region.[7,8] Over 50% of those taking a PPI still had persistent symptoms.[9]

Two contributing factors for the increased prevalence of GERD in females include pregnancy and the presence of NERD.[10] The prevalence of erosive esophagitis is higher in men.[10] Gender is an important factor in the development of Barrett's esophagus and esophageal adenocarcinoma, which are both more common in men. As such, screening for Barrett's esophagus is only considered in men, except in unique circumstances, such as women with scleroderma and esophageal involvement.[11] Adenocarcinoma of the esophagus is more common in those with chronic GERD symptoms than those who do not have GERD. The relationship of adenocarcinoma with Barrett's esophagus, or long-standing GERD symptoms (as an independent risk factor for esophageal adenocarcinoma), remains to be clearly defined.

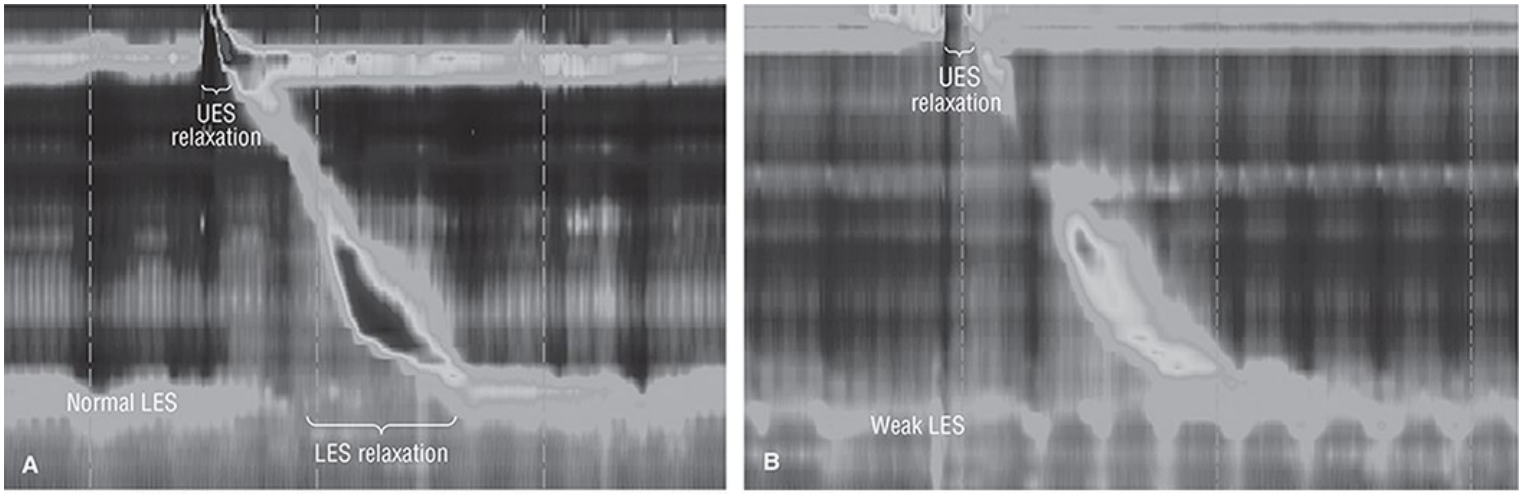
Established risk factors that may contribute to the development or worsening of GERD symptoms include obesity, tobacco smoking, and genetic predisposition.[12] Obesity is associated with a 2.5 times increased risk for developing GERD.[13] Tobacco smoking may increase the prevalence of GERD 1.26 times compared to nonsmokers.[6] Other risk factors or comorbidities for GERD include alcohol consumption, certain medications and foods, respiratory diseases, and reflux chest pain syndrome. More recently, nonalcoholic fatty liver disease and major depressive disorder have been reported as worsening GERD symptoms.[14]

PATHOPHYSIOLOGY

The key factor in the development of GERD is the abnormal reflux of gastric contents from the stomach into the esophagus, oral cavity, and/or the lung.[1] An incompetent antireflux barrier at the esophagogastric junction (EGJ) plays a major role in GERD pathophysiology.[3] In some cases, gastroesophageal reflux is associated with defective lower esophageal sphincter (LES) pressure or function (Fig. 50-1). Patients may have decreased gastroesophageal sphincter pressures related to (a) spontaneous transient LES relaxations (TLESRs), (b) transient increases in intra-abdominal pressure, or (c) an atonic LES, all of which may lead to the development of gastroesophageal reflux. Problems with other normal mucosal defense mechanisms, such as abnormal esophageal anatomy, improper esophageal clearance of gastric fluids, reduced mucosal resistance to acid, delayed or ineffective gastric emptying, inadequate production of epidermal growth factor, and reduced salivary buffering of acid, may also contribute to the development of GERD. Substances that may promote esophageal damage on reflux into the esophagus include gastric acid, pepsin, bile acids, and pancreatic enzymes. Thus, the composition and the volume of the refluxate, as well as duration of exposure, are important aggressive factors in determining the consequences of gastroesophageal reflux.

FIGURE 50-1

Normal versus weak lower esophageal sphincter pressure and relaxations via high resolution manometry.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The presence of an "acid pocket" is a potential explanation for postprandial reflux symptoms and may represent a target for treatment of reflux disease. While gastric acidity is buffered by food, ambulatory pH reflux monitoring has shown that this buffering effect may vary in different parts of the stomach and esophagus. The acid pocket is thought to be an area of unbuffered acid in the proximal stomach that accumulates after a meal and may contribute to GERD

symptoms postprandially.[15] It occurs due to meal-stimulated acid not mixing well with the chyme in the proximal stomach. Gastric secretions form a distinct layer above the chyme. GERD patients are predisposed to upward migration of acid from the acid pocket. In addition, the acid pocket may also be positioned above the diaphragm in patients, especially in those with hiatal hernia, which increases the risk for acid reflux.

Lower Esophageal Sphincter Pressure

The LES is a specialized thickening of the smooth muscle lining of the distal esophagus with an elevated basal resting pressure.[13] The sphincter is normally in a tonic, contracted state, preventing the reflux of gastric material from the stomach, but relaxes on swallowing to permit the passage of food into the stomach. There are three mechanisms by which defective LES pressure may cause gastroesophageal reflux. First, and probably most importantly, reflux may occur following spontaneous TLESRs that are not associated with swallowing. Although the exact mechanism is unknown, esophageal distension, vomiting, belching, and retching cause relaxation of the LES. While not thought to contribute significantly to erosive esophagitis, these transient relaxations, which are normal postprandially, may play an important role in symptom-based esophageal reflux syndromes. Transient decreases in sphincter pressure are responsible for more than half of the reflux episodes in patients with GERD. The propensity to develop gastroesophageal reflux secondary to transient decreases in LES pressure is probably dependent on numerous factors, including the degree of sphincter relaxation, efficacy of esophageal clearance, patient position (more common in recumbent position), gastric volume, and intragastric pressure. Second, reflux may occur following transient increases in intra-abdominal pressure (stress reflux). An increase in intra-abdominal pressure such as that occurring during straining, bending over, coughing, eating, or a Valsalva maneuver may overcome a weak LES, and thus may lead to reflux. Third, the LES may be atonic, thus permitting free reflux as seen in patients with scleroderma.

Various foods and medications may aggravate esophageal reflux by decreasing LES pressure or by precipitating symptomatic reflux by direct mucosal irritation (Table 50-1). Pregnancy is a condition in which reflux is common. There are many postulated reasons for the increased incidence of heartburn during pregnancy, including hormonal effects on esophageal muscle, LES tone, and physical factors (increased intra-abdominal pressure) resulting from an enlarging uterus. A decrease in LES pressure resulting from any of the previously mentioned causes is not always associated with gastroesophageal reflux. Likewise, individuals who experience decreases in sphincter pressures and subsequently reflux do not always develop GERD. The other natural defense mechanisms (anatomic factors, esophageal clearance, mucosal resistance, and other gastric factors) must be evoked to explain this phenomenon.

TABLE 50-1

Foods and Medications That May Worsen GERD Symptoms

Foods/Beverages	Medications
Decreased Lower Esophageal Sphincter Pressure	
Fatty meal	Anticholinergics
Carminatives (peppermint, spearmint)	Barbiturates
Chocolate	Caffeine
Coffee, cola, tea	Dihydropyridine calcium channel blockers
Garlic	Dopamine
Onions	Estrogen
Chili peppers	Nicotine
Alcohol	Nitrates
	Progesterone
	Tetracycline
	Theophylline
Direct Irritants to the Esophageal Mucosa	
Spicy foods	Aspirin
Orange juice	Bisphosphonates
Tomato juice	Nonsteroidal anti-inflammatory drugs
Coffee	Iron
Tobacco	Quinidine
	Potassium chloride

Anatomic Factors

Disruption of the normal anatomic barriers by a hiatal hernia (when a portion of the stomach protrudes through the diaphragm into the chest) was once thought to be a primary etiology of gastroesophageal reflux and esophagitis. Now it appears that a more important factor related to the presence or absence of symptoms in patients with hiatal hernia is the LES pressure. Patients with hypotensive LES pressures and large hiatal hernias are more likely to experience gastroesophageal reflux following abrupt increases in intra-abdominal pressure compared with patients with a hypotensive LES and no hiatal hernia.

Esophageal Clearance

In many patients with GERD, the problem is not that they produce too much acid but that the acid spends too much time in contact with the esophageal mucosa. Contact time is dependent on the rate at which the esophagus clears the noxious material, as well as the frequency of reflux. Swallowing contributes to esophageal clearance by increasing salivary flow. Saliva contains bicarbonate that buffers the residual gastric material on the surface of the esophagus. The production of saliva decreases with increasing age, making it more difficult to maintain a neutral intraesophageal pH. In addition, swallowing is decreased during sleep, making nocturnal GERD a problem in many patients.

Mucosal Resistance

Within the esophageal mucosa and submucosa, there are mucus-secreting glands that may contribute to the protection of the esophagus. Bicarbonate moving from the blood to the lumen can neutralize acidic refluxate in the esophagus. When the mucosa is repeatedly exposed to the refluxate in GERD, or if there is a defect in the normal mucosal defenses, hydrogen ions diffuse into the mucosa, leading to the cellular acidification and necrosis that ultimately cause esophagitis. In theory, mucosal resistance may be related not only to esophageal mucus but also to tight epithelial junctions, epithelial cell turnover, nitrogen balance, mucosal blood flow, tissue prostaglandins, and the acid–base status of the tissue. Saliva is also rich in epidermal growth factor, stimulating cell renewal.

Gastric Emptying/Increased Intra-abdominal Pressure

Delayed gastric emptying can contribute to gastroesophageal reflux. An increase in gastric volume may increase both the frequency of reflux and the amount of gastric fluid available to be refluxed. Gastric volume is related to the volume of material ingested, rate of gastric secretion, rate of gastric emptying, and amount and frequency of duodenal reflux into the stomach. Factors that increase gastric volume and/or decrease gastric emptying, such as smoking and high-fat meals, are often associated with gastroesophageal reflux. This partially explains the prevalence of postprandial gastroesophageal reflux. Fatty foods may increase postprandial gastroesophageal reflux by increasing gastric volume, delaying the gastric emptying rate, and decreasing the LES pressure. Patients with gastroesophageal reflux, particularly infants, may have a defect in gastric antral motility. The delay in emptying may promote regurgitation of feedings, which might, in turn, contribute to two common complications of GERD in infants (eg, failure to thrive and pulmonary aspiration).[16]

Increased GERD symptoms and complications occur in obese patients. Obesity is considered an independent risk factor for GERD due to increased intra-abdominal pressure and reduced LES pressure.[17] An increased risk for developing both erosive esophagitis and Barrett's esophagus can be attributed to obesity. A gain in body mass index (BMI) of greater than 3.5 kg/m^2 is associated with increased new-onset GERD symptoms, regardless of baseline BMI.[18] TLESRs, incompetent LES, and impaired esophageal motility have been attributed to obesity.[19,20]

Composition of Refluxate

The composition, pH, and volume of the refluxate are important aggressive factors in determining the consequences of gastroesophageal reflux. If the pH of the refluxate is less than 2, esophagitis may develop secondary to protein denaturation. In addition, pepsinogen is activated to pepsin at this pH and may also cause esophagitis. Duodenogastric reflux esophagitis, or "alkaline esophagitis," refers to esophagitis induced by the reflux of bilious and pancreatic fluid. The term "alkaline esophagitis" may be a misnomer in that the refluxate may be either weakly alkaline or acidic in nature. Although bile acids have both a direct irritant effect on the esophageal mucosa and an indirect effect of increasing hydrogen ion permeability of the mucosa, symptoms are more often related to acid reflux than to bile reflux. Specifically, the percentage of time that the esophageal pH is less than 4 is greater for patients with severe disease as compared with that for patients with mild disease. Nevertheless, the combination of acid, pepsin, and/or bile is a potent refluxate in producing esophageal damage.

The pathophysiology of gastroesophageal reflux is a complex cyclic process. It is difficult, if not impossible, to determine which occurs first: gastroesophageal reflux leading to defective peristalsis with delayed clearing or an incompetent LES pressure leading to gastroesophageal reflux. Understanding the factors associated with the development of GERD provides insight into the treatment modalities currently used to manage patients suffering from this disease.

Complications

Several complications may occur with gastroesophageal reflux, including esophagitis, esophageal strictures, Barrett's esophagus, and esophageal adenocarcinoma. Strictures are common in the distal esophagus and are 1 to 2 cm in length. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) or

aspirin is an additional risk factor that may contribute to the development or worsening of GERD complications. In some patients, the reparative process leads to the replacement of the squamous epithelial lining of the esophagus by specialized columnar-type epithelium (Barrett's esophagus), which increases the incidence of esophageal strictures by as much as 30%. Screening for Barrett's esophagus is indicated in men with chronic GERD symptoms (more than 5 years) and/or heartburn or acid regurgitation occurring at least weekly; and two or more of the following risk factors for Barrett's esophagus or esophageal adenocarcinoma: (1) over 50 years old; (2) White race; (3) central obesity (waist circumference greater than 102 cm or waist-hip ratio greater than 0.9); (4) tobacco use (current or previous use); and (5) family history of Barrett's esophagus or esophageal adenocarcinoma.[21] Women with scleroderma and esophageal involvement may also benefit from screening for Barrett's esophagus.[11] The risk of esophageal adenocarcinoma may be higher for patients with Barrett's esophagus as compared with that for the general population. The annual risk of esophageal adenocarcinoma was 0.2% to 05% in those with nondysplastic Barrett's esophagus.[21] The annual risk of cancer progression increases to 0.7% in those with low-grade dysplasia and as high as 7% in those with high-grade dysplasia.[14,21]

Helicobacter pylori

The role of *H. pylori* status for patients with GERD is uncertain. As a consequence of the controversy surrounding *H. pylori* and GERD, specific guidelines on how to handle patients who are *H. pylori* positive are lacking. Most clinicians would probably opt to eradicate *H. pylori* infections once detected. However, routine screening for *H. pylori* is not recommended as part of the diagnosis and management of GERD. Further studies are needed to determine the role of *H. pylori* for patients with GERD.

CLINICAL PRESENTATION: GERD

1 GERD can be described on the basis of either esophageal symptoms or esophageal tissue injury. The common symptoms include heartburn, regurgitation, chest pain, and dysphagia. Dysphagia and odynophagia are considered alarm symptoms that require further evaluation. The severity or frequency of the symptoms of gastroesophageal reflux does not always correlate with the degree of esophageal tissue injury, but it does correlate with the duration of reflux. The clinical presentation of GERD overlaps with other conditions such as eosinophilic esophagitis, functional heartburn, and gastroparesis leading to challenges in managing GERD patients.[7] Reflux hypersensitivity may contribute to the patient's perception of symptom severity despite normal esophageal reflux exposure.[15] It is important to distinguish GERD symptoms from those of other diseases.

Diagnostic Tests

The most useful tool in the diagnosis of gastroesophageal reflux is the clinical history, including presenting symptoms and associated risk factors.[1] Patients presenting with typical symptoms of reflux, such as heartburn or regurgitation, do not usually require invasive esophageal evaluation. These patients benefit from an initial empiric trial of acid suppression therapy. A clinical diagnosis of GERD can be assumed in patients who respond to appropriate therapy.[1] However, response to an empiric course of PPI was only 71% sensitive and 44% specific as compared to the combination of endoscopy and ambulatory pH monitoring.[22] This is due to the diverse symptom profile seen in GERD with variable responses to PPIs. PPIs are the most effective in patients with erosive esophagitis and are less effective with regurgitation, extraesophageal symptoms, gastroparesis, achalasia, eosinophilic esophagitis, reflux hypersensitivity, or functional gastrointestinal (GI) disorders. A strategy based on symptom domain and assessment of esophageal function testing may better define therapy.[23] The presence of erosive esophagitis (grade B, C, or D) or Barrett's esophagus per endoscopy, or abnormal pH testing defines "proven" GERD.[24] In addition having a "proven" diagnosis of GERD helps limit PPI use to those who are most likely to respond and avoid unnecessary adverse effects such as renal failure, enteric infections, vitamin/mineral deficiencies, bone fractures, and hypomagnesemia.[22,23] Proven GERD should be established before long-term acid suppression therapy is considered. In the case of functional heartburn, eosinophilic esophagitis, reflux hypersensitivity, or other nonreflux GI disorders, acid suppression therapy may not be the most appropriate choice for treatment as these are not acid-related disorders.

Diagnostic evaluation is useful to prevent misdiagnosis, identify complications, and assess treatment failures.[20] Diagnostic tests should be performed in those patients who do not respond to therapy and in those who present with alarm symptoms (eg, dysphagia, odynophagia, and weight loss), which may be more indicative of complicated disease. Additional diagnostic testing can help stratify patients with GERD into management categories that help guide clinicians to the most appropriate therapy.[24]

2 Useful diagnostic tests for GERD include upper endoscopy, ambulatory reflux (pH) monitoring, combined impedance–pH monitoring, manometry/high-resolution esophageal pressure topography, and impedance manometry. Endoscopy is commonly used to evaluate mucosal injury and to assess for the presence of Barrett's esophagus or other complications, such as strictures or adenocarcinoma. Biopsies are necessary to diagnose Barrett's esophagus. A

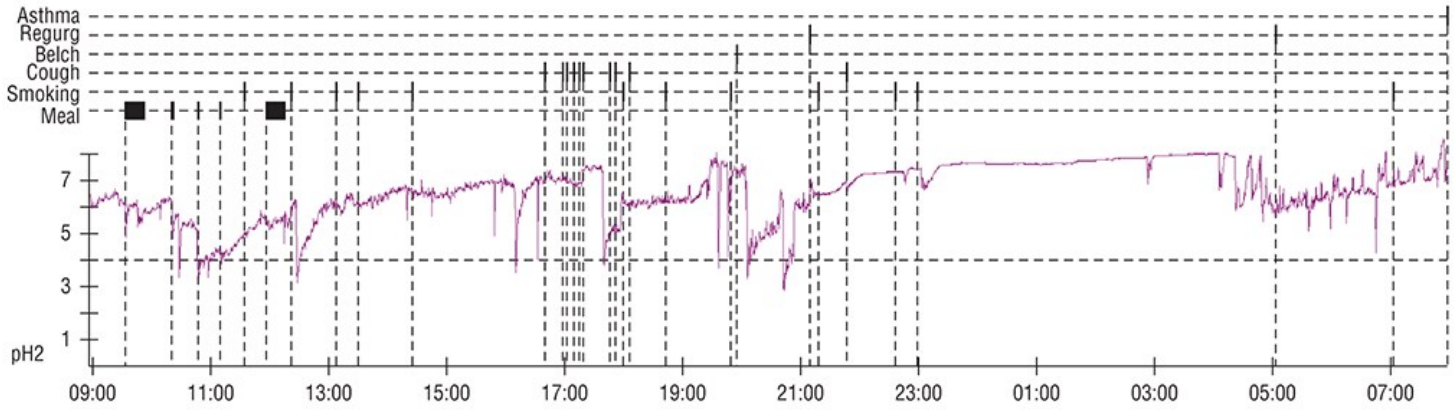
camera-containing capsule swallowed by the patient offers visualizing the esophageal mucosa via endoscopy. This is less invasive than traditional endoscopy and takes less than 15 minutes to perform in the clinician's office, but biopsies cannot be obtained. Unfortunately, the presence or absence of mucosal damage does not prove whether the patient's symptoms are reflux related; for that, ambulatory reflux monitoring is useful.

3 Whereas ambulatory reflux monitoring (24-hour pH monitoring) only measures acid reflux, combined impedance–pH monitoring measures both acid and nonacid reflux. Ambulatory reflux monitoring is performed by passing a small pH probe transnasally and placing it approximately 5 cm above the LES. Patients are asked to keep a diary of symptoms that later are correlated with the pH measurement corresponding to the time the symptom was reported (Fig. 50-2). Approximately 24 hours of data can be obtained using this method. The wireless pH monitoring involves attaching a radiotelemetry capsule to the esophageal mucosa. The advantages of this method are that a longer period of monitoring is possible (48-96 hours), it may demonstrate superior recording accuracy compared with some catheter designs, and it is more comfortable for the patient because a nasogastric tube is unnecessary.[1,22] Ambulatory reflux monitoring is especially useful in patients with symptoms that are refractory to PPIs.[25]

FIGURE 50-2

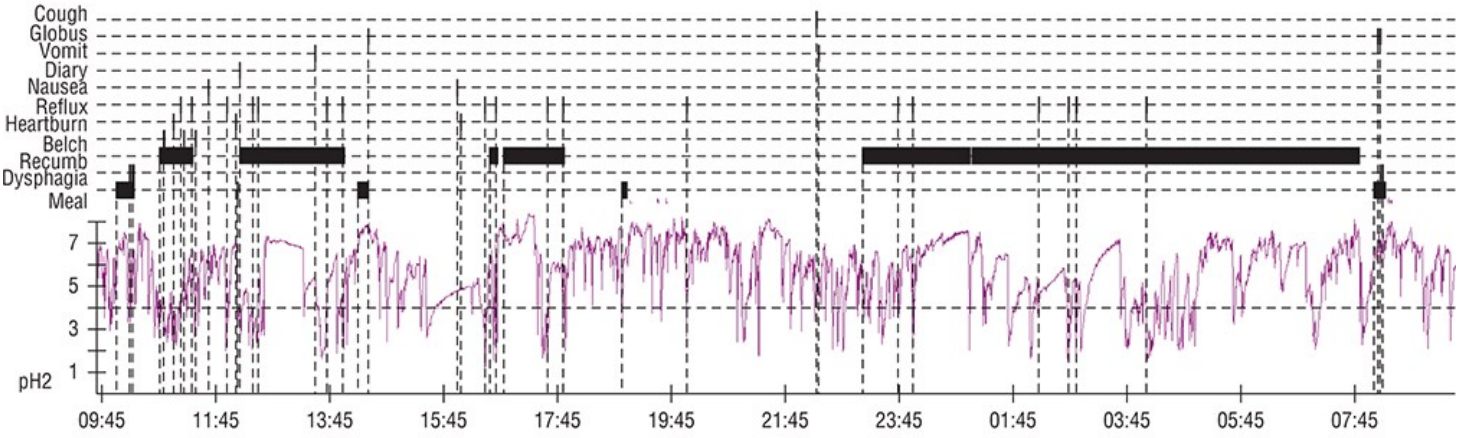
Graphical representation of a normal 24-hour esophageal pH test profile compared to an abnormal 24-hour ambulatory esophageal pH test profile.

A



Normal 24 hour ambulatory esophageal pH test						
	Total	Normal	Upright	Normal	Supine	Normal
• Fraction time pH <4 (%)	1.9	<4.2	1.9	<6.3	0%	<1.2
• Number of refluxes	81		81		0	
• Number of long refluxes (>5 min)	0		0		0	
• Duration of longest reflux (min)	2.3		2.3		0	
• Time pH <4 (min)	25.9		25.9		0	

B



Abnormal 24-hour ambulatory esophageal pH test						
	Total	Normal	Upright	Normal	Supine	Normal
• Fraction time pH <4 (%)	16	<4.2	10.6	<6.3	20.6	<1.2
• Number of refluxes	332		143		189	
• Number of long refluxes (>5 min)	10		6		4	
• Duration of longest reflux (min)	7.9		7.1		7.9	
• Time pH <4 (min)	220.5		66.8		153.7	

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Clinical Presentation: GERD Syndromes[1,22,26-28]

Symptom-Based GERD Syndromes (With or Without Esophageal Tissue Injury)

Typical symptoms (may be aggravated by activities that worsen gastroesophageal reflux such as recumbent position, bending over, or eating a meal high in fat):

- Heartburn (hallmark symptom described as a substernal sensation of warmth or burning rising up from the abdomen that may radiate to the neck; may be waxing and waning in character)
- Regurgitation/belching
- Reflux chest pain

Alarm symptoms (these symptoms may be indicative of complications of GERD such as Barrett's esophagus, esophageal strictures, or esophageal adenocarcinoma and require further diagnostic evaluation):

- Dysphagia (common)
- Odynophagia
- Bleeding
- Weight loss

Tissue Injury-Based GERD Syndromes (With or Without Esophageal Symptoms)

Symptoms (may present with alarm symptoms such as dysphagia, odynophagia, or unexplained weight loss):

- Esophagitis
- Esophageal strictures
- Barrett's esophagus
- Esophageal adenocarcinoma

Extraesophageal GERD Syndromes

These symptoms have an association with GERD, but causality should only be considered if a concomitant esophageal GERD syndrome is also present:

- Chronic cough
- Laryngitis
- Wheezing
- Asthma (~50% with asthma have GERD)

Diagnostic Tests for GERD

Clinical History

- Used to make a clinical diagnosis of GERD in patients with typical symptoms.

Endoscopy

- Preferred for assessing mucosal injury and complications. Biopsies are needed to identify Barrett's esophagus, adenocarcinoma, and eosinophilic esophagitis (a nonacid-related esophageal disorder that does not respond well to acid suppression therapy).
- Indications for endoscopy: (1) persistent or progressive GERD symptoms despite appropriate therapy; (2) presence of dysphagia or odynophagia; (3)

unexplained weight loss of more than 5%; (4) presence of GI bleeding and strictures; (5) screening for Barrett's esophagus in high-risk patients; (6) placement of wireless pH monitoring; (7) prior to endoscopic or surgical antireflux procedures or after procedures in those with recurrent symptoms.[26]

- Note: Noninflammatory GERD and major motor disorders may be missed by endoscopy.

Ambulatory Reflux Monitoring With or Without Impedance

- Useful for (a) patients not responding to acid suppression therapy when endoscopy is normal; (b) those with atypical/extraesophageal symptoms; or (c) those contemplating surgery.
- Assesses the acid exposure time (AET) and frequency of reflux episodes and helps determine if symptoms are acid-related.
  - An AET of less than 4% is considered normal, while greater than 6% is considered abnormal.[22]
  - Less than 40 reflux episodes in a 24-hour period is considered normal, while more than 80 reflux episodes per 24-hour period is considered abnormal.
- Reflux hypersensitivity is defined as positive symptom association in the absence of breakthrough acid.[27]
- Monitoring without impedance measures only acid reflux; adding impedance measures both acid and nonacid reflux
  - Testing patients off PPI therapy is recommended (1) to evaluate the AET in patients with normal endoscopy or low-grade esophagitis and no previously positive pH testing and (2) in those considering antireflux surgery.[22]
  - Testing patients on double-dose PPI therapy is recommended in patients with (1) prior Los Angeles grade C or D esophagitis; (2) long segment Barrett's esophagus; or (3) prior abnormal ambulatory pH monitoring. In these cases, pH–impedance monitoring is recommended to correlate refractory symptoms with reflux episodes or to identify inadequate acid suppression.

Manometry/High-Resolution Esophageal Pressure Topography

- Useful in those who have failed twice-daily PPI therapy with normal endoscopic findings to identify motor disorders, to evaluate peristaltic function in those who are candidates for antireflux surgery, and to assure proper placement of pH probes. Tubeless pH monitoring using endoscopic landmarks for placement may negate the need for manometry for ensuring proper placement of esophageal pH probes.

Impedance Manometry

- Evaluates bolus transit esophageal clearance/retention.
- Evaluates LES and UES pressures and peristalsis.

Empiric Proton Pump Inhibitor as a Diagnostic Test for GERD

- Less expensive and more convenient than ambulatory reflux monitoring but lacks standardized dosing regimen and duration of the diagnostic trial. This is not recommended as a diagnostic tool.

Barium Radiography

- Not routinely used to diagnose GERD because it lacks sensitivity and specificity; cannot identify Barrett's esophagus. Can detect hiatal hernia.

TREATMENT

Therapeutic modalities used in the treatment of gastroesophageal reflux are targeted at reversing the various pathophysiologic abnormalities.

Desired Outcomes

4 The goals of treatment are to (a) alleviate or eliminate the patient's symptoms and improve health-related quality of life, (b) decrease the frequency or

recurrence and duration of gastroesophageal reflux, (c) promote healing of the injured mucosa, and (d) prevent complications. Therapy is directed at augmenting defense mechanisms that prevent reflux and/or decrease the aggressive factors that worsen reflux or mucosal damage. Therapy is directed at (a) decreasing the acidity of the refluxate, (b) decreasing the gastric volume available to be refluxed, (c) improving gastric emptying, (d) increasing LES pressure, (e) enhancing esophageal acid clearance, and (f) protecting the esophageal mucosa.

General Approach to Treatment

5 GERD treatment is determined by disease severity and includes: (a) lifestyle changes and patient-directed therapy with antacids, nonprescription H2RAs, and/or nonprescription PPIs; (b) pharmacologic treatment with prescription-strength acid suppression therapy; (c) surgery; and (d) endoscopic therapies (Table 50-2).[1,29] The initial therapeutic modality used is in part dependent on the patient's condition (frequency of symptoms, degree of esophagitis, and presence of complications) (Table 50-3). A step-down approach, starting with a PPI, instead of an H2RA, is most often advocated. Once esophageal healing has occurred or symptoms improved, patients should be stepped down to the lowest effective dose of PPI or switched to an H2RA. The clinician should determine the most appropriate approach for the individual patient. Every attempt should be made to aggressively control symptoms and to prevent relapses early in the course of the patient's disease in order to prevent the complications. For patients with moderate-to-severe GERD, especially those with erosive disease, starting with a PPI as initial therapy is advocated because of its superior efficacy over H2RAs.

TABLE 50-2

Evidence-Based Treatment Recommendations for GERD in Adults

Recommendation	Level of Evidence and Strength of Evidence[a]
Lifestyle Modifications	
• Weight loss in overweight GERD patients or those who have recently gained weight.	Moderate, Conditional
• Elevation of the head end of the bed and avoidance of food 2-3 hours before bedtime if nocturnal GERD symptoms present.	Low, Conditional
• Routine elimination of foods that can trigger reflux is not recommended in the treatment of GERD.	Low, Conditional
Acid Suppression Therapy	
• Therapy of choice for symptom relief and healing of erosive esophagitis is an 8-week PPI course. There is similar efficacy among all PPIs.	High, Strong
• For maximal pH control, delayed-release PPIs should be administered 30-60 minutes before meals.	Moderate, Strong
• PPIs should be started at once-daily dosing prior to the first meal each day.	Moderate, Strong
• Patients with Barrett's esophagus can be treated similarly to those with GERD who do not have Barrett's esophagus.	Moderate, Strong
• Flexibility with meal-time administration may be seen with newer PPIs (eg, dexlansoprazole).	Moderate, Conditional
• When clinically indicated, PPIs are considered safe in pregnancy.	Moderate, Conditional
• Adjustments of dose timing and/or twice-daily dosing may be beneficial in patients with night-time symptoms, variable	Low, Strong

schedules, and/or sleep disturbances who are partial responders to PPI therapy.	
• In patients with typical GERD symptoms who also have extraesophageal symptoms, a PPI trial is recommended.	Low, Strong
• Optimization of PPI therapy should be assessed in anyone with refractory GERD symptoms.	Low, Strong
• Increasing to twice-daily dosing or switching PPI may be beneficial in partial responders to PPI therapy.	Low, Conditional
• Further evaluation is recommended for nonresponders to PPI therapy.	Low, Conditional
• If adverse effects occur with PPI, may consider switching to an alternative PPI.	Low, Conditional
• Patients with osteoporosis can use a PPI.	Moderate, Conditional
• Concern for hip fracture with PPI should be considered in those with osteoporosis AND other risk factors for hip fracture.	Moderate, Conditional
• PPIs are a risk factor for development of *Clostridium difficile.*	Moderate, Moderate
• PPIs are a risk factor for development of community-acquired pneumonia with short-term use (but not long-term use).	Moderate, Conditional
• PPIs can be used in patients on clopidogrel, and there is not an increased risk for adverse cardiovascular events.	High, Strong
Promotility Therapy and Other Nonacid Suppression Therapies	
• Prokinetic medications and/or baclofen should not be used to manage GERD without diagnostic evaluation.	Moderate, Conditional
• Sulcralfate is not recommended in nonpregnant GERD patients.	Moderate, Conditional
Maintenance Therapy	
• Maintenance therapy is recommended for (1) patients with continued symptoms after PPI discontinuation and (2) patients with complications including erosive esophagitis and Barrett's esophagus.	Moderate, Strong
• The lowest effective dose should be used when long-term PPI therapy is indicated for maintenance. Strategies such as on-demand and intermittent therapy may be beneficial.	Low, Conditional
• H2RAs may be used as maintenance therapy in patients without erosive disease when the goal is heartburn relief.	Moderate, Conditional
Surgery	
• Antireflux surgery is a long-term treatment option in GERD patients.	High, Strong
• Antireflux surgery is not recommended in PPI nonresponders.	High, Strong

• Antireflux surgery is not recommended in patients with extraesophageal symptoms not responding to PPI therapy.	Moderate, Strong
• Endoscopic therapy or transoral incisionless fundoplication not recommended as alternative to medical or traditional surgical procedures.	Moderate, Strong
• Bariatric surgery (gastric bypass) should be considered in obese patients contemplating surgical therapy.	Moderate, Conditional

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

[a]Level of evidence per Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system: High = further research not likely to change authors' confidence in the estimate of effect; Moderate = further research would likely have an impact on the confidence in the estimate of effect; Low = further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the evidence. Strength of evidence per GRADE system: Strong = desired effects of an intervention clearly outweigh the undesirable effects; Conditional = there is uncertainty about the trade-offs between desirable effects and undesirable effects.

Data from References 1 and 29.

TABLE 50-3

Therapeutic Approach to GERD in Adults

Recommended Treatment Regimen	Oral Dose	Comments
Intermittent, mild heartburn (individualized lifestyle modifications + patient-directed therapy with antacids and/or nonprescription H2RAs *or* nonprescription PPIs)		
Individualized lifestyle modifications		Lifestyle modifications should be individualized for each patient.
Patient-directed therapy with antacids (12 years of age or older)		
Magnesium hydroxide/aluminum hydroxide with simethicone	10-20 mL as needed or after meals and at bedtime	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention; do not exceed 16 teaspoonfuls per 24 hours.
Antacid/alginic acid	2-4 tablets or 10-20 mL after meals and at bedtime	Note: Content of alginic acid varies greatly among products; the higher the alginic acid the better (at least 500 mg).
Calcium carbonate	500 mg, 2-4 tablets as needed	
Patient-directed therapy with nonprescription H2RAs (up to twice daily) (12 years of age or older)		
Cimetidine	200 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention.
Famotidine	10-20 mg	

Nizatidine	75 mg	
Patient-directed therapy (over 18 years old) with nonprescription PPIs (taken once daily)		
Esomeprazole	20 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention.
Lansoprazole	15 mg	
Omeprazole	20 mg	
Omeprazole/sodium bicarbonate	20 mg/1,100 mg	
Symptomatic relief of GERD (individualized lifestyle modifications + prescription-strength H2RAs *or* prescription-strength PPIs)		
Individualized lifestyle modifications		Lifestyle modifications should be individualized for each patient.
Prescription-strength H2RAs		
Cimetidine (off-label use)	400 mg four times daily or 800 mg twice daily	• For typical symptoms, treat empirically with prescription-strength acid suppression therapy. • If symptoms recur, consider maintenance therapy. Note: Most patients will require standard doses for maintenance therapy.
Famotidine	20 mg twice daily	
Nizatidine	150 mg twice daily	
Prescription-strength PPIs		
Dexlansoprazole	30 mg once daily for 4 weeks	• For typical symptoms, treat empirically with prescription-strength acid suppression therapy. • Patients with moderate-to-severe symptoms should receive a PPI as initial therapy. • If symptoms recur, consider maintenance therapy.
Esomeprazole	20-40 mg once daily	
Lansoprazole	15 mg once daily	
Omeprazole	20 mg once daily	
Omeprazole/sodium bicarbonate	20 mg once daily	
Pantoprazole (Off-label use)	40 mg once daily	
Rabeprazole	20 mg once daily	
Healing of erosive esophagitis or treatment of patients with moderate-to-severe symptoms or complications (individualized lifestyle modifications + high-dose H2RAs *or* PPIs *or* antireflux surgery)		
Individualized lifestyle modifications		Lifestyle modifications should be individualized for each patient.

PPIs (up to twice daily for up to 8 weeks)		
Dexlansoprazole	60 mg daily	• For extraesophageal or alarm symptoms, obtain endoscopy with biopsy to evaluate mucosa. • If symptoms are relieved, consider maintenance therapy. PPIs are the most effective maintenance therapy for patients with extraesophageal symptoms, complications, and erosive disease. Start with twice-daily PPI therapy if reflux chest syndrome is present. • Patients not responding to pharmacologic therapy, including those with persistent extraesophageal symptoms, should be evaluated via manometry and/or ambulatory reflux monitoring.
Esomeprazole	20-40 mg daily	
Lansoprazole	30 mg once or twice daily	
Omeprazole	20 mg once or twice daily	
Rabeprazole	20 mg once or twice daily	
Pantoprazole	40 mg once or twice daily	
High-dose H2RAs (for 8-12 weeks)		
Cimetidine	400 mg four times daily or 800 mg twice daily	Note: If high-dose H2RA is needed, may consider using PPI to lower cost, increase convenience, and increase tolerability. Note: Four times daily H2RA is considered off-label use for nizatidine.
Famotidine	20-40 mg twice daily	
Nizatidine	150 mg two to four times daily	
Interventional therapy		
Antireflux surgery Bariatric surgery Endoscopic therapies		

While weight loss in obese patients and elevation of the head end of the bed are beneficial for most GERD patients, recommending all lifestyle modifications to all patients is not recommended.[1] Instead, education on lifestyle modifications should be tailored to the individual needs of the patient. Table 50-4 lists some of the lifestyle modifications that can be recommended on an individualized basis.

TABLE 50-4

Nonpharmacologic Treatment of GERD with Lifestyle Modifications

- Elevate the head end of the bed (increases esophageal clearance). Use 6- to 8-inch (15-20 cm) blocks under the head side of the bed.
- Weight reduction (reduces symptoms) in obese patients.
- Avoid foods that may decrease lower esophageal sphincter pressure or increase transient lower esophageal sphincter relaxation (fats, chocolate, alcohol, peppermint, and spearmint).
- Include protein-rich meals in diet (augments lower esophageal sphincter pressure).
- Avoid foods that have a direct irritant effect on the esophageal mucosa (spicy foods, orange juice, tomato juice, and coffee).
- Behaviors that may reduce esophageal acid exposure.
- Eat small meals and avoid sleeping immediately after meals (sleep after 3 hours if possible; decreases gastric volume).
- Stop smoking (decreases spontaneous esophageal sphincter relaxation).
- Avoid alcohol (increases amplitude of the lower esophageal sphincter, peristaltic waves, and frequency of contraction).
- Avoid tight-fitting clothes.
- Always take drugs in the sitting upright or standing position and with plenty of liquid, especially for those that have a direct irritant effect on the esophageal mucosa (eg, bisphosphonates, tetracyclines, quinidine, potassium chloride, iron salts, aspirin, nonsteroidal anti-inflammatory drugs).

Data from Reference 20.

6 Patients with typical GERD symptoms should be treated with lifestyle modifications as appropriate and a trial of empiric acid suppression therapy. Those who do not respond to empiric therapy or who present with alarm symptoms such as dysphagia, weight loss, or GI bleeding should undergo endoscopy. Acid suppression therapy with PPIs or H2RAs is the mainstay of GERD treatment. Patients presenting with moderate-to-severe symptoms (with or without esophageal erosions) should be started on a PPI as initial therapy because it provides the most rapid symptomatic relief and healing in the highest percentage of patients.[1] H2RAs in divided doses are effective for patients with milder GERD symptoms. However, when standard doses of H2RA therapy are not effective at relieving symptoms, it is more cost effective and efficacious to switch to a PPI.

Promotility agents (such as metoclopramide) are not as effective as acid suppression agents. Combining a promotility agent with acid suppression medications offer only modest improvements in symptoms over standard doses of H2RAs and should not be routinely recommended. In addition, the availability of a promotility agent that has an acceptable adverse effect profile is lacking. Mucosal protectants, such as sucralfate, have a limited role in the treatment of GERD.

Maintenance therapy may be necessary to control symptoms and to prevent complications. For patients with more severe symptoms (with or without esophageal erosions) or for patients with other complications, maintenance therapy with a PPI is most effective. Routine use of combination therapy is not recommended in GERD maintenance therapy. In cases of refractory GERD, the diagnosis should be confirmed through further diagnostic tests before long-term, high-dose acid suppression therapy is considered.[1]

Nonpharmacologic Therapy

Nonpharmacologic treatment of GERD includes lifestyle modifications, antireflux surgery, bariatric surgery (in obese patients), and endoscopic therapies.

Lifestyle Modifications

The most common lifestyle modifications for GERD include weight loss in obese patients and elevation of the head end of the bed, especially for those patients who have symptoms while in a recumbent position.[1] Other lifestyle modifications should be individualized based on the patient's specific situation. These include consumption of smaller meals and not sleeping for at least 3 hours after eating, avoidance of foods or medications that exacerbate GERD, smoking cessation, avoidance of tight-fitting clothes, and avoidance of alcohol (see Table 50-4).[30]

Obesity increases the risk of GERD symptoms and complications including Barrett's esophagus. There is a clear association between BMI, waist circumference, and weight gain.[1] Surprisingly, weight gain in those considered to have a normal BMI is also associated with new onset GERD symptoms.[1] Even more alarming is the potential association between BMI and cancer in the esophagus and gastric cardia.[1] A high-fat meal will decrease LES pressure for

2 hours or more postprandially. In contrast, a high-protein, low-fat meal will elevate LES pressure. A weight loss goal of at least 10% is recommended to help to improve GERD symptoms.[30]

Elevating the head end of the bed by approximately 6 to 8 inches (15-20 cm) with a foam wedge under the mattress (not just elevating the head with pillows) decreases nocturnal esophageal acid contact time and should be recommended. In general, anything that improves sleep hygiene may reduce GERD symptoms because TLESRs are reduced during sleep.[31] Many foods have been linked to worsening GERD symptoms; however, the evidence is weak for this association. Some foods decrease LES pressure (eg, fats and chocolates), while other foods can act as direct contact irritants to the esophageal mucosa (citrus juice, tomato juice, coffee, and pepper) (see Table 50-1).

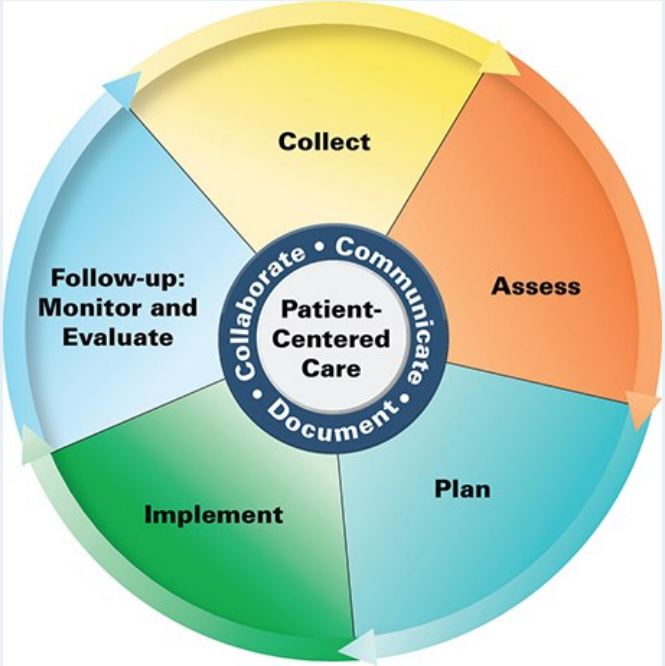
Evaluate patient profiles to identify potential medications that may exacerbate GERD symptoms (see Table 50-1). Some medications decrease LES pressure, while other medications can act as direct contact irritants to the esophageal mucosa. Proper patient education can help prevent dysphagia or esophageal ulceration. Closely monitor patients for worsening symptoms when any of these medications are started. If symptoms worsen, alternative therapies may be warranted. Clinicians must weigh the risks and benefits of continuing a medication known to worsen GERD and esophagitis.

Smoking can cause aerophagia (eg, air swallowing), which leads to increased belching and regurgitation. Patients with GERD should be encouraged to quit smoking because it may be a risk factor for Barrett's esophagus and esophageal adenocarcinoma.[21] Alcohol decreases LES pressure and may exacerbate symptoms such as heartburn.

Many patients are noncompliant with lifestyle modifications, and even those who do comply continue to have symptoms that require acid suppression therapy. Nonetheless, it is important to stress the potential benefits of lifestyle modifications that would benefit each individual patient.

PATIENT CARE PROCESS

Patient Care Process for the Management of Gastroesophageal Reflux Disease



Collect

- Patient characteristics (eg, age, race, sex, weight, BMI, pregnant)
- Patient history (past medical, family, social, dietary habits, tobacco use)
- Health literacy and barriers to medication access

- Thorough history of prescription, nonprescription, and natural medication use
- Medication allergies and intolerances (including actual reaction to medication)
- Laboratory results for major organ function (eg, SCr to calculate CrCL, liver enzymes to assess hepatic function)

Assess

- Assess major organ function (eg, creatinine clearance, hepatic impairment)
- Determine the type, frequency, duration of symptoms, and identify exacerbating factors
- Identify alarm symptoms or extraesophageal symptoms that require further diagnostic evaluation by clinician (see section "Clinical Presentation")
- Review lifestyle factors, including foods that may be contributing to symptoms (see Table 50-1)
- Review medication profile for medications that may be contributing to symptoms (see Table 50-1) and potential drug–drug interactions
- Assess what has been done so far (including medications and lifestyle modifications)
- Establish goals of therapy and if they are currently being met (see section "Desired Outcomes")
- Assess the appropriateness and effectiveness of current GERD regimen

Plan*

- Identify individualized lifestyle modifications that may improve symptoms (see Table 50-4)
- Determine appropriate therapy (may include both nonpharmacologic and pharmacologic) based on patient's presentation (see Table 50-2)
- For pharmacologic therapy, include medication name, dose, route, frequency, and duration of therapy recommendation (see Table 50-3)
- Establish monitoring parameters for safety (eg, drug–drug, drug–food, drug–disease, and drug–lab interaction checking; short- and long-term adverse effects, and prevention of complications)
- Establish monitoring parameters for efficacy (eg, resolution of symptoms, improvement of symptoms, and healing of injured mucosa) (see Table 50-5)
- Identify patient education that may be needed (eg, purpose of medication, individualized lifestyle modifications, adverse effects, administration clinical pearls, adherence, potential need for long-term maintenance therapy, and so on)
- For refractory symptoms, seek potential causes such as medication adherence, timing of medication, drug interactions, nonacid related disorders, and so on
- Screen for symptoms that would require further diagnostic evaluation from clinician (eg, alarm symptoms, atypical symptoms, or complications)

Implement*

- Counsel patient on individualized lifestyle modifications that may improve symptoms (eg, elevating head of the bed with a wedge, weight management, and so on) (see Table 50-4)
- Initiate appropriate nonpharmacologic and pharmacologic therapy based on patient presentation (see Tables 50-2 and 50-3)
- Recommend additions, modifications, or discontinuations to therapy based on patient response
- Provide patient education with regard to disease state, lifestyle modifications, and treatment plan. Counsel patient on (a) what causes GERD and things to avoid; (b) when to take their medication (eg, 30 minutes before meal); (c) what potential adverse effects (including long-term adverse effects) or drug interactions may occur

- Use motivational interviewing techniques to maximize medication adherence
- Schedule follow-up as appropriate

Follow-up: Monitor and Evaluate

- Follow-up after 8 to 16 weeks to assess effectiveness of acid-suppression therapy. Recommend alternative therapy when necessary; attempt to deprescribe PPIs if possible
- Monitor patient for safety goals established above
- Evaluate the need for maintenance therapy based on patient presentation and response to therapy
- Assess improvement in quality-of-life measures such as physical, psychological, and social functioning and well-being
- Evaluate patient for the presence of adverse drug reactions, complications or new drug–drug interactions
- Stress the importance of medication adherence to treatment plan to patient as indicated

**Collaborate with patient, caregivers, and other healthcare professionals.*

Interventional Approaches

Interventional approaches include antireflux surgery, bariatric surgery, magnetic sphincter augmentation, and endoscopic therapies. These are discussed in more detail below.

Antireflux Surgery

The goal of antireflux surgery is to reestablish the antireflux barrier, to position the LES within the abdomen where it is under positive (intra-abdominal) pressure, and to close any associated defect in the diaphragmatic hiatus by reinforcing the crural muscles. Surgical intervention is a viable alternative treatment for select patients. It is indicated when (1) long-term pharmacologic management is undesirable, (2) persistent proven GERD symptoms or esophageal mucosal damage despite appropriate pharmacologic therapy, and (3) significant EGJ disruption (eg, hiatal hernia).[22] Antireflux surgery does not impact the progression of Barrett's esophagus to esophageal adenocarcinoma.[13] The most common antireflux surgery performed is laparoscopic Nissen fundoplication. Patients should undergo ambulatory reflux pH monitoring and manometry prior to antireflux surgery.[31] Patients with typical symptoms who are responsive to PPIs and those with abnormal ambulatory pH monitoring showing positive correlation with GERD symptoms show the most benefit from antireflux surgery, while those with extraesophageal symptoms show a lower response to antireflux surgery. The major complications with antireflux surgery include gas bloat syndrome (inability to belch or vomit), dysphagia, vagal denervation, and splenic trauma. Long-term effectiveness of antireflux surgery is uncertain.[33]

Success of antireflux surgery in patients with PPI-refractory heartburn depends on careful screening and ruling out nonacid related causes of heartburn, such as eosinophilic esophagitis, achalasia, and biliary disease. Seventy-eight percent of the patients with "refractory GERD" evaluated did not have reflux-related disease. Instead, they had non-GERD esophageal disorders or functional heartburn. In those who were PPI-refractory and had reflux-related heartburn, surgery was superior to medical treatment (67% versus 12%-28%, respectively).[34]

Bariatric surgery, specifically laproscopic Roux-en-Y gastric bypass, should be considered in obese patients (BMI greater than 35 kg/m^2) contemplating surgery.[1] The consideration of bariatric surgery in obese patients for improvement of GERD symptoms is a result of the proposed difference in pathophysiology in this patient population. Abdominal pressure may play a greater role in the development of GERD in obese patients. Reflux symptoms were decreased from 31% to 5%, esophagitis was decreased from 24% to 10%, and incidence of GERD was decreased from 34% to 12% with laparoscopic Roux-en-Y gastric bypass surgery in morbidly obese patients.[13]

Magnetic Sphincter Augmentation

This minimally invasive alternative to antireflux surgery involves surgically implanting a ring of titanium-encased magnets at the EGJ to improve lower

esophageal resistance and reduce symptoms of GERD.[24,35] Long-term effectiveness of magnetic sphincter augmentation is uncertain.

Endoscopic Therapies

Endoscopic therapies are less invasive than surgical fundoplication and aim for a similar efficacy. Two endoscopic therapies are radiofrequency ablation of the LES and endoscopic suturing of the LES (transoral incisionless fundoplication). Radiofrequency ablation is recommended in patients with Barrett's esophagus with esophageal high-grade dysplasia. Guidelines also acknowledge radiofrequency ablation as a treatment option in low-grade dysplasia.[21] Transoral incisionless fundoplication creates a valve at the EGJ and is beneficial in patients with chronic GERD with abnormal ambulatory pH monitoring or low-grade erosive esophagitis with either no hiatal hernia or a hiatal hernia less than or equal to 2 cm.[31] However, it was less effective than laparoscopic Nissen fundoplication.[36]

Pharmacologic Therapy

Pharmacologic treatment consists of (a) patient-directed therapy with nonprescription antacids, H2RAs, or PPIs and (b) prescription-strength acid suppression therapy, or (c) promotility medications. Because of clinical similarities to other GI disorders, such as functional heartburn, eosinophilic esophagitis, and reflux hypersensitivity, which are not acid-related disorders, "proven" GERD should be diagnosed prior to committing a patient to long-term acid suppression therapy. Considering alternative therapies may be more appropriate for these non-GERD indications that may be more affiliated with modulating effects of anxiety or visceral and central hypersensitivity.[3]

Patient-Directed Therapy

Patient-directed therapy, where patients self-treat themselves with nonprescription medications, is appropriate for mild, intermittent symptoms. Patients with continuous symptoms lasting longer than 2 weeks should seek medical attention.[4] Self-treatment without further evaluation should also be avoided when the duration of severe or nocturnal heartburn exceeds 3 months, patient is symptomatic while taking prescription strength acid suppression therapy, or in the presence of alarm symptoms.[4]

Antacids and Antacid–Alginic Acid Products

Patients should be educated that antacids are an appropriate component of treating milder GERD symptoms, even though documentation of their efficacy in placebo-controlled clinical trials is lacking. Antacids may offer immediate symptomatic relief and help maintain the intragastric pH greater than 4, which decreases the activation of pepsinogen to pepsin, a proteolytic enzyme. The neutralization of gastric fluid may also lead to increased LES pressure. Patients who require frequent use of antacids for chronic symptoms should be treated with prescription strength acid suppression therapy.

Some antacid products are combined with alginic acid, which is not a potent-neutralizing agent and does not enhance LES pressure; however, it does form a highly viscous solution or "raft" that floats on the surface of the gastric contents. This viscous solution serves as a protective barrier for the esophagus against reflux of gastric contents and reduces the frequency of the reflux episodes. The alginic acid "raft" can adapt to the acid pocket, continuously floating above newly secreted acid near the EGJ. The combination product may be superior to antacids alone in relieving the symptoms of GERD.[37] There was a significant benefit favoring alginate therapy when compared to antacids in GERD; however, with moderate heterogeneity.[37] Alginate may also improve symptoms in patients on once-daily PPI still having residual reflux symptoms.[38] Liquid containing sodium alginate 1,000 mg/20 mL was more effective than an antacid without sodium alginate in controlling esophageal acid exposure after meals.[39] Efficacy data indicating endoscopic healing are lacking. There are many products with varying amounts of alginic acid. Some of the products contain lower amounts of alginic acid or list alginic acid under inactive ingredients with no amounts specified. Products with a higher alginic acid component are preferred (eg, 500 mg or higher amount of alginc acid). Patients should be encouraged to check medication labels for ingredients.

Antacid or antacid combination products interact with a variety of medications by altering gastric pH, increasing urinary pH, adsorbing medications to their surfaces, providing a physical barrier to absorption, or forming insoluble complexes with other medications. Antacids have clinically significant drug interactions with tetracycline, ferrous sulfate, isoniazid, sulfonylureas, and quinolone antibiotics. Antacid–drug interactions are influenced by composition, dose, dosage schedule, and formulation of the antacid. They may also cause constipation or diarrhea depending on the magnesium or aluminum content.

Dosage recommendations for antacids in the management of GERD are somewhat difficult to derive from the literature. Doses range from hourly to an as-needed basis (see Table 50-3). In general, antacids have a short duration of action, which necessitates frequent administration throughout the day to provide continuous neutralization of acid. Taking antacids after meals can increase the duration of action from about 1 to 3 hours; however, nighttime acid

suppression cannot be maintained with bedtime doses.

Nonprescription H2RAs and Proton Pump Inhibitors

Nonprescription H2RAs (cimetidine, famotidine, and nizatidine) are effective in diminishing gastric acid secretion when taken prior to meals and decrease GERD symptoms associated with exercise. Antacids may have a slightly faster onset of action, while the H2RAs have a much longer duration of action compared with antacids.

The PPIs esomeprazole, omeprazole (alone or combined with sodium bicarbonate), and lansoprazole are available without a prescription for the short-term treatment of heartburn.

Acid Suppression Therapy

8 Acid suppression is the mainstay of GERD treatment. PPIs provide the greatest symptom relief and the highest healing rates, especially for patients with erosive disease, moderate-to-severe symptoms, or complications.

Proton Pump Inhibitors

PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole [with or without sodium bicarbonate], pantoprazole, and rabeprazole) block gastric acid secretion by inhibiting gastric H^+/K^+-adenosine triphosphatase in gastric parietal cells. This produces a profound, long-lasting antisecretory effect capable of maintaining the gastric pH greater than 4, even during postprandial acid surges. A correlation exists between the percentage of time the gastric pH remains greater than 4 during the 24-hour period and healing erosive esophagitis.

The efficacy in treating GERD is similar among all of the PPIs.[31] Symptomatic relief is seen in approximately 83% of patients with endoscopic evidence of injury after 8 weeks treated with a PPI, whereas the endoscopic healing rate at 8 weeks is 78%.[1] Symptom response to NERD is less robust with approximately 60% of patients experiencing complete relief with PPI therapy.[1] PPIs are superior to H2RAs in treating moderate-to-severe GERD and should be given empirically to those with troublesome symptoms. This includes not only patients with esophageal tissue injury (eg, Barrett's esophagus, strictures, or esophagitis) but also patients with symptom-based GERD syndromes. Patients with uncomplicated GERD who respond well to a short-term course of PPI therapy should attempt to discontinue or to lower to the lowest effective dose.[40,41] Rebound acid hypersecretion may occur when PPIs are withdrawn making deprescribing of PPIs difficult. While no specific deprescribing or tapering regimen is recognized, strategies could include tapering dose down over 4 to 6 weeks, on-demand dosing, or abrupt discontinuation. One approach is to lower the dose by going from twice daily to once daily or halving the dose; or stopping the PPI and using an on-demand-regimen.[42] Up to 30% of patients on long-term PPI therapy could discontinue use and up to 80% were able to lower the dose.[43] PPI on-demand dosing was just as effective as low dose maintenance therapy for GERD symptoms.[44,45] Abrupt discontinuation of PPI therapy, while not ideal due to increased risk of rebound GERD symptoms, could be a reasonable option in select patients.

Twice-daily PPI use is indicated in those not responding to a standard once-daily course of therapy. Before increasing the frequency to twice daily, optimization of PPI therapy should be assessed (eg, taken 30-60 minutes prior to largest meal each day). In patients who are partial responders to initial PPI therapy, a trial of an alternative PPI may also be considered. Either strategy (twice-daily PPI or switching to an alternative PPI) has resulted in about a 20% improvement in symptoms with neither strategy demonstrating a clear advantage.[1] Partial response may also be due to abnormal patient perception, altered motility, or impaired LES dynamics where adjunctive therapy addressing the underlying cause may be helpful.[46] Patients with Barrett's esophagus should be treated similar to patients without Barrett's esophagus.[1] Further diagnostic evaluation is indicated for patients not responding to twice-daily PPI therapy.

The most common adverse effects associated with PPIs include headache, diarrhea, nausea, and abdominal pain. Increasing concerns regarding PPI safety continue to be reported. Community-acquired pneumonia may occur with short-term use in GERD patients.[1] Enteric infections, vitamin B12 deficiency, hypomagnesemia, and bone fractures are potential long-term adverse effects associated with PPIs (Table 50-5).[28,40,47,48] Gastric acidity plays an important role in the absorption of minerals such as calcium and magnesium, as well as with vitamin B12. While PPIs do not have a direct effect on the pH in the colon, they do have a downstream effect on colonic bacteria increasing the risk for *Clostridioides difficile* infections.[40,48] There is no evidence to support the use of probiotics in patients on long-term PPIs to prevent infection.[40] Despite potential concerns, data are lacking to recommend calcium, vitamin B12, or magnesium intake above the recommended daily allowance, unless there are other risk factors that warrant additional supplementation. Likewise, routine screening or monitoring of bone mineral density, serum creatinine, magnesium, or vitamin B12 levels are not recommended just because the patient is on

long-term PPI therapy.[40] Another concern is chronic kidney disease. Proposed mechanisms for kidney injury include repeated bouts of acute interstitial nephritis, concurrent NSAID use, diabetes, and hypomagnesemia. Chronic kidney disease occurred in 3.68% of patients started on a PPI over a 5-year period compared to 2.56% in patients on an H2RA (Hazard ratio [HR] = 1.28). No association between PPI use and myocardial infarction has been clearly demonstrated.[48]

TABLE 50-5

Drug Monitoring

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Antacids			
Magnesium hydroxide/aluminum hydroxide Antacid/alginic acid Calcium carbonate	• Diarrhea or constipation (depending on product) • Alterations in mineral metabolism • Acid–base disturbances	• Periodic calcium and phosphate levels in patients on chronic therapy	• Use caution with aluminum- and calcium-containing antacids in patients with renal impairment • Aluminum-containing antacids may bind to phosphate in the gut and lead to bone demineralization
H2RAs			
Cimetidine Famotidine Nizatidine	• Headache, somnolence, fatigue, dizziness, and either constipation or diarrhea	• Monitor for CNS effects, especially in older patients	• May see increased CNS effects (rare) in those over 50 years of age or in those with renal or hepatic dysfunction • May be associated with vitamin B12 deficiency with longer duration therapy and in higher doses
Proton Pump Inhibitors			
Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Omeprazole/sodium bicarbonate Pantoprazole Rabeprazole	*Most common adverse effects:* • Headache, dizziness, diarrhea, flatulence, abdominal pain, and nausea *Other important adverse effects:* • Enteric infections • Community-acquired pneumonia *Long-term adverse*	• Number and type of diarrhea episodes • Periodic magnesium levels warranted in those on higher doses or who are on therapy for greater than 1 year • Routine bone density studies or calcium supplementation should only be considered if other risk factors for osteoporosis or bone fractures are present • Respiratory symptoms within first 30 days of therapy • Periodic (not routinely) vitamin B12 serum concentration with long-term use	• Acid suppression may result in loss of host defense against ingested spores and bacteria permitting a higher burden of exposure • Hypomagnesemia is uncommon but can be serious; more likely in those on PPIs greater than 1 year • May increase risk for osteoporosis-related fractures of the hip, wrist, or spine; most common with high-dose (eg, multiple daily doses) and long-term use (eg, more than 1 year) and patients with osteoporosis can remain on PPI • PPIs may inhibit secretion of intrinsic factor, which potentially can lead to vitamin B12 deficiency; this is not common and usually associated with use for greater than 3 years • May increase risk of community-acquired pneumonia, particularly within the first 30 days of therapy

	effects: • Hypomagnesemia • Bone fractures • Vitamin B12 deficiency • Chronic kidney disease		

Data from References 28, 40, 47, and 48.

An increased risk of PPI-induced hepatic encephalopathy has been suggested.[48] The mechanism of this toxicity is related to alterations in the gut microbiota. Hypochlorhydria may lead to small bowel bacterial overgrowth which may contribute to hepatic adverse events. The risk of dementia or cognitive decline in patients receiving PPIs has raised concerns in the lay press; however, the evidence for this association is weak.[40] Vitamin B12 deficiency and enhanced beta-amyloid levels are potential contributing factors related to the potential cognitive decline associated with PPI use.[48]

Most of this data on these long-term adverse events are from observational studies and results have been variable. The first and largest prospective, randomized trial that examined PPI safety for up to 3 years found no difference in most adverse outcomes previously associated with long-term PPI use.[49] The one outcome that occurred more often in the PPI group was non-*Clostridioides difficile* enteric infections. Based on the results of this trial, limiting use of PPIs due to concerns regarding long-term effects is not warrented.[49] Overuse of PPI should still be minimized until the clinical implications of chronic therapy are better elucidated as more patients remain on PPI therapy for more than 3 years. Best practice advice from the American Gastroenterology Association states there is no convincing evidence to rank PPI formulations on potential risks.[40] More importantly, changing the paradigm to a more individualized approach to diagnosing GERD has been advocated based on careful assessment of anatomy, motor function, reflux burden, and symptomatic phenotype as a strategy to reduce the overuse of PPIs.[22] Clinicians should strive to identify a clear indication for PPI use before long-term therapy is considered. Deprescribing PPIs to reduce the potential for long-term adverse effects is important. Proper patient education should be done to ensure that appropriate patients are selected for PPI dose reductions or discontinuations to avoid adverse outcomes.[50,51]

Drug interactions with the PPIs vary slightly with each agent. All PPIs can decrease the absorption of medications such as ketoconazole or itraconazole, which require an acidic environment to be absorbed. Concerns have been raised regarding the concomitant use of PPIs, particularly omeprazole, with clopidogrel since it is the strongest inhibitor of CYP2C19.[52] Clopidogrel, a prodrug, is converted to its active metabolite via the CYP2C19 and CYP3A4 enzymes. Inhibition of CYP2C19 by PPIs, specifically omeprazole, may possibly decrease the effectiveness of clopidogrel.

Another consideration, particularly with omeprazole, is the potential polymorphic gene variations seen in the hepatic activity of CYP2C19. This is especially true for patients who are considered “slow metabolizers” of omeprazole, which is not only more common in Asian patients but also found in approximately 3% of White patients. Unfortunately, it is unclear which patients have the polymorphic gene variation that makes them slow metabolizers. Like omeprazole, the metabolism of esomeprazole may also be altered for patients with this polymorphic gene variation. Despite these concerns, there are certain patients with upper GI bleeding or those with multiple risk factors for GI bleeding who require antiplatelet therapy would benefit from PPI therapy. Risk factors for GI bleeding include advanced age, use of anticoagulants, steroids or NSAIDs, presence of *H. pylori*, or previous history of bleeding or peptic ulcer disease complications.[53] For patients on clopidogrel, using an alternative acid suppression agent, such as an H2RA, or a PPI other than omeprazole and esomeprazole or using an alternative antiplatelet agent may be an acceptable alternative if there are concerns.

The PPIs degrade in acidic environments and therefore are formulated in a delayed-release capsule or tablet formulation. Dexlansoprazole, esomeprazole, lansoprazole, and omeprazole contain enteric-coated (pH-sensitive) granules in a capsule form. Dexlansoprazole is unique in that the capsule is a dual delayed-release formulation, with the first release occurring 1 to 2 hours after the dose and the second release occurring 4 to 5 hours after the dose. The clinical significance of this dual release is to allow the medication to have a longer lasting benefit, at least 16 to 18 hours. Patients taking pantoprazole or rabeprazole should be instructed not to crush, chew, or split the delayed-release tablets.

For patients who are unable to swallow the capsule or tablet, or for pediatric patients, there are several alternative administration methods available. The contents of the delayed-release capsules can be mixed in applesauce or placed in orange juice. If a patient has a nasogastric tube, the contents of an omeprazole capsule can be mixed in 8.4% sodium bicarbonate solution. Esomeprazole granules can be dispersed in water. Esomeprazole, omeprazole, and pantoprazole are also available in a delayed-release oral suspension powder packet, while lansoprazole is available as a delayed-release, orally

disintegrating tablet. Esomeprazole and pantoprazole are available in an IV formulation, which offers an alternative route of administration for patients who are unable to take an oral PPI. Importantly, the IV product is not more efficacious than oral PPIs and is significantly more expensive. The IV product should not be routinely used in GERD.

Omeprazole is also available as a delayed-release tablet and in a combination product with sodium bicarbonate as an immediate-release capsule and oral suspension. This is the only immediate-release PPI, and it should be taken on an empty stomach at least 1 hour before a meal. Omeprazole powder for oral suspension offers an alternative to the delayed-release capsules, or IV formulation in adult patients with a nasogastric tube. The immediate-release capsule should be swallowed whole and not opened, sprinkled on food, or administered via nasogastric tube. The 20- and 40-mg immediate-release capsules have the same amount of sodium bicarbonate; therefore, two 20-mg capsules cannot be substituted for a 40-mg capsule.

Patients should be instructed to take their PPI in the morning, 30 to 60 minutes before breakfast or before their biggest meal of the day, to maximize efficacy. Dexlansoprazole can be taken without regard to meals. Patients with nocturnal symptoms may benefit from taking their PPI prior to the evening meal. If dosed twice daily, the second dose should be administered approximately 10 to 12 hours after the morning dose and prior to a meal or snack.

H2RAs

H2RAs (cimetidine, famotidine, and nizatidine) in divided doses are effective in treating patients with mild-to-moderate GERD.[1]

The efficacy of H2RAs in the management of GERD is extremely variable and is frequently lower than desired. Response to the H2RAs is dependent on the (a) severity of disease, (b) dosage regimen used, and (c) duration of therapy. These factors are important when comparing clinical trials and/or assessing a patient's response to therapy. The severity of esophagitis at baseline has a profound impact on the patient's response to H2RAs. For symptomatic relief of mild GERD, low-dose, nonprescription H2RAs or standard doses given twice daily may be beneficial. Patients who do not respond to standard doses may be hypersecreters of gastric acid and will require higher doses. Although higher doses of H2RAs may provide higher symptomatic and endoscopic healing rates, limited information exists regarding the safety of these regimens, and they can be less effective and more costly than once-daily PPIs. Unlike duodenal ulcer disease, in which the duration of therapy is relatively short (eg, 4-6 weeks), prolonged courses of H2RAs are frequently required in the treatment of GERD.

Because all of the H2RAs have similar efficacy, selection of the specific agent to use in the management of GERD should be based on factors such as differences in pharmacokinetics, safety profile, and cost. Patients should be monitored for the presence of adverse effects, as well as potential drug interactions, especially when taking cimetidine. Cimetidine may inhibit the metabolism of theophylline, warfarin, phenytoin, nifedipine, and propranolol, among others. An alternate H2RA should be selected if the patient is on any of these medications. Headache, fatigue, dizziness, and constipation/diarrhea are the most common adverse effects associated with the use of H2RAs. Tachyphylaxis commonly occurs with H2RAs rendering them ineffective after a period of time in some patients. Ranitidine was taken off the US market in 2020 due to contamination with N-nitrosodimethylamine. The age of the product and storage temperatures were noted to accelerate production of this contaminant linked to cancer.

Promotility Agents

Promotility agents may be useful as an adjunct to acid suppression therapy for patients with a known motility defect (eg, LES incompetence, decreased esophageal clearance, and delayed gastric emptying). Unfortunately, all available promotility agents are fraught with undesirable adverse effects and are not as effective as acid suppression therapy.

Metoclopramide

Metoclopramide, a dopamine antagonist, increases LES pressure in a dose-related manner and accelerates gastric emptying in gastroesophageal reflux patients. However, it does not improve esophageal clearance. Metoclopramide provides symptomatic improvement for some patients with GERD; however, substantial data supporting endoscopic healing are lacking. In addition, metoclopramide's adverse effect profile, including extrapyramidal effects, tardive dyskinesia, and other central nervous system (CNS) effects, limits its usefulness in treating many patients with GERD. The risk of adverse effects is much greater for older patients and for patients with renal dysfunction because the drug is primarily eliminated by the kidneys. Contraindications include Parkinson's disease, mechanical obstruction, concomitant use of other dopamine antagonists or anticholinergic agents, and pheochromocytoma.

Bethanechol

Bethanechol, a promotility drug, has limited value in the treatment of GERD because of unwanted adverse effects, such as urinary retention, abdominal discomfort, nausea, and flushing. It is not routinely recommended for the treatment of GERD.

Mucosal Protectants

Sucralfate, a nonabsorbable aluminum salt of sucrose octasulfate, has limited value in the treatment of GERD. It may not be useful in the routine treatment of acid reflux but may be useful in the management of radiation esophagitis and bile or nonacid reflux GERD.

Combination Therapy

Combination therapy with an acid suppression agent and a promotility agent or a mucosal protectant agent would seem logical given the multifactorial nature of the disease, particularly in light of the disappointing results seen with many monotherapy regimens. However, data to support combination therapy are limited, and this approach should not routinely be recommended unless a patient has GERD plus motor dysfunction occurring. The effectiveness of the addition of an H2RA at bedtime to PPI therapy for the treatment of nocturnal symptoms may decrease over time due to tachyphylaxis with H2RAs. Therefore, “as needed” use of bedtime H2RA may be a more appropriate approach if combination with a PPI is deemed necessary. Using the omeprazole–sodium bicarbonate immediate-release product in addition to once-daily PPIs may offer an alternative for nocturnal GERD symptoms.

Maintenance Therapy

9 Many patients with GERD will relapse if medication is withdrawn; therefore, long-term maintenance treatment may be required. A PPI is the drug of choice for maintenance of patients with moderate-to-severe GERD, erosive disease, or other complications such as Barrett’s esophagus. Patients who have symptomatic relapse following discontinuation of therapy or lowering of medication doses should be considered for long-term maintenance therapy to prevent complications or worsening of esophageal function.[1]

In patients with uncomplicated GERD who respond to short-term PPI therapy, lowering the PPI dose or discontinuing the PPI should be considered. If this is not possible, ambulatory reflux pH with or without impedance monitoring should be performed to assure symptoms are GERD-related prior to committing to lifelong PPI use.[40] Patients receiving chronic PPI therapy should be periodically evaluated to assure the lowest possible effective dose is used.[40,60] The goal of maintenance therapy is to improve quality of life by controlling the patient’s symptoms and preventing complications. Patients should be counseled on the importance of complying with lifestyle changes and long-term maintenance therapy in order to prevent recurrence or worsening of disease. H2RAs may be an effective maintenance therapy for patients with mild disease.[1] Low doses of a PPI or alternate-day dosing may be effective in some patients with mild symptoms, thereby allowing dose reduction in some cases. “On-demand” or intermittent maintenance therapy, by which patients take their PPI only when they have symptoms, may be effective for patients with endoscopy-negative GERD.[1,31] Many patients with only mild-to-moderate symptoms may decide on their own to use “on-demand” for the financial benefit and patient satisfaction.[31] However, patients with persistent symptoms and/or complications require standard doses of PPIs.

Studies evaluating the efficacy of the H2RAs in maintaining patients with GERD in remission have been disappointing. No currently available H2RA regimen is FDA-approved for maintenance of healing of erosive esophagitis. Antireflux surgery may also be considered a viable alternative to long-term drug therapy for maintenance of healing for patients who are candidates.

Special Populations

There are several special populations that should be considered when discussing GERD, such as patients with extraesophageal symptoms, pediatric patients, older patients, and patients with refractory symptoms.

Patients with Extraesophageal GERD

Extraesophageal symptoms (such as asthma, laryngitis, or chest pain) should prompt investigation for other possible causes outside of GERD. Because there are many causes of asthma and laryngeal symptoms, a concomitant esophageal GERD syndrome must also be present to associate these symptoms with GERD. A trial of PPI therapy is recommended for those with extraesophageal symptoms with concurrent typical GERD symptoms. Patients with extraesophageal symptoms without typical GERD symptoms should undergo ambulatory reflux monitoring prior to initiation of PPI therapy. If symptoms continue, patients should be evaluated with manometry or ambulatory reflux monitoring with or without impedance to rule out dysmotility or refractory symptoms, respectively.[1] Ambulatory reflux monitoring while on PPI is useful for those with “proven” GERD while testing while off PPI is useful when the goal is to identify moderate-to-severe reflux at baseline.[54]

In patients with chronic cough suspected to be reflux related, lifestyle modifications are recommended.[55] Acid suppression therapy is unlikely to be

beneficial if heartburn or regurgitation is not also present. If the patient does have concomitant heartburn or regurgitation with a chronic cough, PPI therapy may be beneficial but may take up to 3 months before resolution of cough.[55] After 3 months, more diagnostic evaluation is needed.

Pediatric Patients with GERD

Many infants have physiologic reflux with little or no clinical consequence. Uncomplicated gastroesophageal reflux usually manifests as regurgitation or "spitting up" and resolves without incident by about 12 months of life.[16] When evaluating a child for GERD, conduct a history and physical examination. If alarm signs are present, clinicians should tailor testing to address the alarm signs and refer appropriately. If no alarm signs are present, lifestyle and dietary education should be initiated. Symptoms usually respond to supportive therapy, including dietary adjustments, postural management, and reassurance for the parents. Thickened feedings may be useful in milder cases. While this does not decrease reflux episodes, it may decrease the incidence of regurgitation.[16] This strategy of thickening feedings may be appropriate for full-term infants; however, may be associated with necrotizing enterocolitis in preterm infants. Chronic vomiting associated with gastroesophageal reflux must be distinguished from other causes, such as neurologic, metabolic, eating, and rumination disorders. Smaller, more frequent feedings may be beneficial. In formula-fed infants, an extensively hydrolyzed protein may help identify milk protein sensitivity as the cause of unexplained GERD-like symptoms, likewise, exclusion of milk and eggs in the maternal diet for breastfeeding infants may be appropriate.[16] Additionally, a trial of an amino acid-based formula should occur prior to a trial of acid suppression therapy. If lifestyle and dietary education do not resolve the GERD symptoms, a 4- to 8-week trial of acid suppression therapy is recommended.[16] Once a 4- to 8-week course is complete, referral to a pediatric GI specialist is recommended if symptoms are not improved or recur upon weaning therapy.[16]

Developmental immaturity of the LES is one suspected cause of gastroesophageal reflux in infants. Like adults, TLESRs seem to be the most common cause of gastroesophageal reflux in children. Other causes include impaired luminal clearance of gastric acid, neurologic impairment, and type of infant formula. Complications, although rare, include distal esophagitis, failure to thrive, esophageal peptic strictures, Barrett's esophagus, and pulmonary disease. Further diagnostic evaluation is indicated in all who experience apnea or an apparent life-threatening event.

The benefits of using promotility medications, such as metoclopramide, erythromycin, bethanechol, and baclofen, are outweighed by the potential adverse effects that may occur and, therefore, cannot be routinely recommended.[16] Careful consideration should be made before medication is recommended, especially in children younger than 1 year of age.

PPI use in children is increasing, especially in those with esophagitis. Most patients will respond to once-daily PPI dosing. In infants with reflux-related esophagitis, the use of PPIs is the first-line treatment option.[16] Table 50-6 details indications and dosing of PPIs in pediatric patients. Dexlansoprazole and pantoprazole have not been adequately studied in younger pediatric patients. When examining adverse effect data from currently available trial data the authors noted that overall PPI therapy was well tolerated with mostly mild-to-moderate adverse effects in the short term. Adverse effects with individual agents included diarrhea, abdominal pain, and vomiting with headache noted in older age groups and upper and lower respiratory tract infections noted in infants. Long-term use of a PPI without a clear diagnosis of GERD is not recommended.[16]

TABLE 50-6

Oral Proton Pump Inhibitor Therapy in Pediatric Patients

Drug	Indication	Age	Recommended Oral Dose (daily)	
Dexlansoprazole	Symptomatic GERD, erosive esophagitis	≥12 years ≥12 years		30 mg 60 mg
Esomeprazole	Erosive esophagitis	1 month-1 year	3-5 kg	2.5 mg
			>5-7.5 kg	5 mg
			>7.5	10 mg
		1-11 years	<20 kg	10 mg
			≥20 kg	10-20 mg

		≥12 year		20-40 mg
	Symptomatic GERD		<20 kg	10 mg
			>20 kg	20 mg
Lansoprazole	Symptomatic GERD	Infants >3 months		7.5 mg twice daily or 15 mg daily
		1-11 years	≤30 kg >30 kg	15 mg 30 mg
		≥12 year		15 mg
	Erosive esophagitis	Infants >3 months		7.5 mg twice daily or 15 mg daily
		1-11 years	≤30 kg >30 kg	15-30 mg
		≥12 year		30 mg
Omeprazole	GERD, erosive esophagitis, maintenance of healing of erosive esophagitis	≥1 year	5 to <10 kg	5 mg
			10 to <20 kg	10 mg
			≥20 kg	20 mg
Pantoprazole	Symptomatic GERD			1-2 mg/kg/day
	Erosive esophagitis	≥5 years	≥15 to <40 kg	20 mg
			≥40 kg	40 mg
Rabeprazole	Symptomatic GERD	1-11 years	<15 kg	5-10 mg
			≥15 kg	10 mg
		≥12 years		20 mg

*Note: Omeprazole also has dosing for treatment of erosive esophagitis in infants 3 kg to <5 kg of 2.5 mg daily. Otherwise, dosing is the same for children and adolescents for all GERD indications.

Duration of therapy depends on age and indication.

Data from Reference 56.

Older Patients with GERD

Many older patients have decreased host defense mechanisms, such as saliva production. In addition, they have more comorbidities, medications, and physiologic changes that put them at higher risk. Often these patients do not seek medical attention because they feel their symptoms are part of the normal aging process. They may also present with atypical symptoms such as chest pain, asthma, poor dentition, or jaw pain. Decreased GI motility is a common problem in older patients. Unfortunately, there are no good promotility agents available to these patients. Older patients are especially sensitive to the CNS effects of metoclopramide. They may also be sensitive to the CNS effects of H2RAs. PPIs appear to be the most useful treatment modality, because they have superior efficacy and are dosed once daily, which is beneficial in all patients, but is especially beneficial in the older population. Long-term risk of bone fractures may be of concern in this population. Patients at risk for bone fractures should be monitored appropriately.

Patients with Refractory GERD

What constitutes refractory GERD is not well defined. Prior to increasing the dose to twice daily, adherence and proper administration timing of PPI therapy should be optimized. Refractory GERD should be considered in patients who have not responded to a standard course of twice-daily PPI therapy over a 12-week period. The most likely causes associated with PPI-refractory GERD include: (1) abnormal acid reflux despite PPI therapy; (2) reflux hypersensitivity where physiologic (normal) reflux causes symptoms; (3) esophageal disorders other than GERD (eg, achalasia); (4) extraesophageal disorders (eg, lung disease or heart disease); and (5) functional heartburn.[57,58] In some situations, variations in drug metabolism in certain patients may contribute to refractory GERD. Switching to another PPI or increasing the dose to twice daily may be beneficial; however, the latter may reduce compliance.[31] Rabeprazole is least affected by CYP enzymes and improves acid suppression in patients considered to be slow metabolizers of CYP 2C19.[57] Reeducating patients regarding lifestyle modifications is recommended.[31] Manometry or ambulatory esophageal reflux monitoring is useful for patients who are not responding to therapy who have normal endoscopic findings.

Patients with Los Angeles Grade C or D esophagitis, peptic stricture, Barrett's esophagus or pathologic acid exposure seen on ambulatory reflux pH monitoring (while off PPI) indicate "proven" GERD. These patients should undergo ambulatory reflux pH-impedance monitoring while on PPI therapy to determine if they are truly PPI-refractory or if contents are nonacidic in nature.[57] PPI-refractory GERD is associated with esophageal exposure time greater than 6% on PPI.[57] AET represents the percentage of time the esophageal pH is less than 4 over the monitoring period. If AET is normal then consider other non-GERD causes such as functional heartburn or reflux hypersensitivity. Patients with hypersensitive esophagus or functional heartburn do not respond as well to acid suppression therapy.[2]

The majority of patients with refractory symptoms experience nocturnal acid breakthrough. Dexlansoprazole offers greater dosing flexibility since it does not need to be administered with food so may provide effective control of nocturnal symptoms.[59] Likewise, omeprazole-sodium bicarbonate immediate-release products can be given without regard to meals and may be useful in controlling nocturnal symptoms.[59]

Antireflux surgery, magnetic sphincter augmentation, and endoscopic therapies may have a role in refractory GERD, depending on the scenario. If ambulatory reflux monitoring tests are negative, the patient is unlikely to have GERD and PPI therapy should be discontinued and alternative diagnosis should be investigated.[1] Baclofen may be beneficial for patients with residual acid or weakly acidic reflux by decreasing TLESRs, although with potential adverse effects seen in some patients.[31] Functional heartburn or reflux hypersensitivity may be treated with tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or trazodone.[5,31] Eosinophilic esophagitis or dysmotility syndromes are causes of nonacid-related esophageal symptoms and require therapies other than a PPI.[31,60]

EVALUATION OF THERAPEUTIC OUTCOMES

The long-term benefits of treatment are difficult to assess because of the limited information known about the epidemiology and natural history of GERD. Consequently, successful outcomes are measured in terms of three separate end points: (a) relieving symptoms, (b) healing the injured mucosa, and (c) preventing complications.

10 The short-term goal of therapy is to relieve symptoms such as heartburn and regurgitation to the point at which they do not impair the patient's quality of life. Patients should be educated regarding specific lifestyle modifications that are applicable to their individual situation including weight loss and raising the head end of the bed. Patient medication profiles should be reviewed for medications that may aggravate GERD. Patients should be monitored for adverse drug reactions and potential drug interactions. Deprescribing PPIs or tapering to the lowest effective dose is a key strategy in preventing adverse effects. Table 50-5 reviews common adverse drug reactions and monitoring of medications used in GERD. The frequency and severity of symptoms should be monitored, and patients should be counseled on symptoms that suggest the presence of complications requiring immediate medical attention, such as

dysphagia. Patients should also be monitored for the presence of extraesophageal symptoms, such as laryngitis asthma or chest pain. These symptoms require further diagnostic evaluation. Long-term maintenance treatment is indicated for patients who have strictures as they commonly recur if reflux esophagitis is not treated.

The second goal is to heal the injured mucosa. Again, individualized lifestyle modifications and the importance of complying with the therapeutic regimen chosen to heal the mucosa should be stressed. Patients should be educated about the risk of relapse and the need for long-term maintenance therapy to prevent recurrence or complications.

The final, long-term goal of therapy is to decrease the risk of complications (esophagitis, strictures, Barrett's esophagus, and esophageal adenocarcinoma). A small subset of patients may continue to fail treatment despite therapy with high doses of H2RAs or a PPI. Patients should be monitored for the presence of continual pain, dysphagia, or odynophagia.

ABBREVIATIONS

AET	acid exposure time
BMI	body mass index
EGJ	esophagogastric junction
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HR	hazard ratio
H2RA	histamine-2 receptor antagonist
LES	lower esophageal sphincter
NERD	nonerosive reflux disease
NSAID	nonsteroidal anti-inflammatory drug
PPI	proton pump inhibitor
TLESR	transient lower esophageal sphincter relaxation
UES	upper esophageal sphincter

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SELF-ASSESSMENT QUESTIONS

1. Which of the following represents an alarm GERD symptom?

   A. Regurgitation

   B. Chronic cough

   C. Dysphagia

   D. Heartburn

2. A 52-year-old male patient presents to his primary care physician and reports bothersome heartburn symptoms for the last 4 months with occasional regurgitation. The patient reports that the heartburn symptoms are occurring most days of the week. The patient also reports that he has developed painful, difficult swallowing over the last several months. What is the most appropriate recommendation for management of the patient's heartburn symptoms?

   A. Start omeprazole 20 mg daily and recommend antireflux surgery.

   B. Start omeprazole 20 mg daily and recommend endoscopy.

   C. Encourage lifestyle modifications and recommend ambulatory reflux monitoring.

   D. Start omeprazole 20 mg twice daily and recommend manometry.

3. A 42-year-old male patient with typical GERD symptoms occurring 4-5 days per week has been recently initiated on once-daily PPI therapy. The patient reports that his heartburn symptoms are most prominent overnight. The patient has no other medical history, and his BMI is 22 kg/m^2. As per the American College of Gastroenterology guidelines which of the following represents the best lifestyle modification to recommend for this patient?

   A. Elimination of all potential trigger foods in his diet

   B. Reduce protein content in diet

   C. Calorie restriction to lose 10% of his body weight

   D. Elevation of the head of the bed (not with pillows)

4. A 38-year-old women experiencing frequent typical GERD symptoms was initiated on omeprazole once daily. The patient is reporting that her symptoms are less frequent and milder since initiating PPI therapy, but her symptoms remain bothersome. Which of the following is the best recommendation?

   A. Change to ranitidine 150 mg twice daily.

   B. Refer the patient for ambulatory reflux monitoring.

   C. Initiate antacid as needed for breakthrough symptoms.

   D. Change to pantoprazole 40 mg daily.

5. Tachyphylaxis is a limitation to maintenance therapy with which of the following?

   A. Cimetidine

   B. Dexlansoprazole

   C. Calcium carbonate

   D. Metoclopramide

6. Which of the following PPIs utilizes an immediate-release formulation?
   A. Dexlansoprazole
   B. Omeprazole/Sodium bicarbonate
   C. Lansoprazole
   D. Pantoprazole
7. Which of the following drugs is considered a risk factor for the development of bone fractures?
   A. Metoclopramide
   B. Famotidine
   C. Rabeprazole
   D. Alginic acid
8. Endoscopic evaluation is indicated in which of the following patients?
   A. 47-year-old with a 10-year history of typical GERD symptoms well controlled on current proton pump inhibitor
   B. 38-year-old with persistent heartburn after 2-week trial of over-the-counter famotidine 20 mg BID
   C. 40-year-old with persistent typical GERD symptoms on pantoprazole 40 mg BID
   D. 52-year-old with recurrence of symptoms after trial off of esomeprazole 20 mg daily
9. When attempting to discontinue/deprescribe PPI therapy, which of the following is an appropriate recommendation?
   A. Adding an H2RA when the PPI is discontinued
   B. Changing to an immediate-release PPI formulation
   C. Overlapping an H2RA with PPI therapy before discontinuation
   D. Tapering down the dose to the lowest dose that controls symptoms
10. Which therapy has been shown superior in patients with PPI-refractory heartburn?
   A. Antireflux surgery
   B. Radiofrequency ablation
   C. Metoclopramide 10 mg four times daily
   D. Famotidine 10 mg twice daily
11. The preferred initial treatment option for a 45-year-old male presenting with a 1-week history of GERD symptoms is:
   A. Patient-directed therapy with nonprescription omeprazole
   B. Prescription strength PPI
   C. Antireflux surgery
   D. Endoscopic therapy

12. Which of the following regimens would be most appropriate to prevent osteoporosis in a 25-year-old marathon runner on esomeprazole 20 mg daily for typical GERD symptoms?

    A. Calciumcarbonate 1,250 mg three times daily

    B. Calcium citrate 500 mg once daily

    C. Elemental calcium 1.5 grams plus vitamin D 400 units once daily

    D. No calcium indicated since he/she does not have risk factors for osteoporosis

13. Which of the following is a potential adverse effect of long-term PPI therapy?

    A. Hypercalcemia

    B. *Clostridium difficile* infection

    C. Vitamin A deficiency

    D. Hypokalemia

14. Which of the following patients would be most appropriate for a trial of patient-directed over-the-counter PPI therapy?

    A. 37-year-old with 1-year history of dysphagia and odynophagia

    B. 61-year-old with a 5-day history of heartburn and belching

    C. 22-year-old with asthma and chronic cough

    D. 44-year-old with a 3-month history of daily heartburn and regurgitation

15. Which of the following patients is the best candidate for maintenance therapy for GERD?

    A. 37-year-old patient who relapses after an 8-week course of PPI therapy

    B. 31-year-old patient with intermittent GERD symptoms

    C. 52-year-old patient with scleroderma

    D. 2-month-old baby with intermittent regurgitation of feeds

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Examples of alarm GERD symptoms include unexplained weight loss, dysphagia, odynophagia, or bleeding. See section "Clinical Presentation" for a complete discussion on the types of GERD symptoms.

2. **B.** Endoscopy is indicated in patients who present with alarm symptoms such as weight loss, dysphagia, odynophagia, or bleeding. See section "Clinical Presentation" (Diagnostic Tests) section of the chapter for additional information. A standard course of PPI therapy is also warranted.

3. **D.** The American College of Gastroenterology guidelines recommend elevation of the head of the bed and avoidance of meals 2-3 hours before bedtime in patients with nocturnal GERD. Weight loss is recommended in those that are overweight, which this patient is not. Routine global elimination of trigger foods is not recommended, and protein intake should be increased to improve reduced LES pressure. See section "Treatment" (Nonpharmacologic Therapy [Lifestyle Modifications]) of the chapter for more information.

4. **D.** The American College of Gastroenterology guidelines note that in patients with a partial response to PPI therapy that additional benefit may be seen by increasing the PPI to twice daily or trialing an alternative PPI. See section "Treatment" (Pharmacologic Therapy [Acid Suppression Therapy (PPI)]) of the chapter for more information.

5. **A.** Tachyphylaxis can occur with consistent administration of H2RAs. See section "Treatment" (Pharmacologic Therapy [Combination Therapy]) and

(Pharmacologic Therapy [Special Populations (Patients with Refractory GERD)]) of the chapter for more information.

6. **B.** Omeprazole/Sodium bicarbonate is the only PPI available in an immediate-release formulation and it should be taken on an empty stomach at least one hour before a meal.

7. **C.** Proton pump inhibitors have been identified as a risk factor for the development of osteoporosis. See Table -5 Drug Monitoring section in the chapter for more information on monitoring parameters for acid suppressive therapies.

8. **C.** Endoscopy is used to assess for mucosal injury from GERD and to assess for other complications. It should be performed in patients with persistent or progressive GERD symptoms despite appropriate medical therapy. See section "Clinical Presentation" (Diagnostic Tests) of the chapter for more information

9. **D.** There are three strategies that have been studied and deemed reasonable when discontinuing/deprescribing PPI therapy; tapering down the dose, on-demand dosing, and abrupt discontinuation. "Treatment" (Pharmacologic Therapy [Acid Suppression Therapy (PPI)]) of the chapter for more information.

10. **A.** A recent VA study showed that laparoscopic Nissen fundoplication surgery (antireflux surgery) was shown to be superior to continuing PPIs in patients who were properly screened to rule out nonacid related causes of heartburn. More than two thirds of patients showed more than a 50% improvement in symptoms as one year compared to 28% with continued PPI use ($p = 0.007$). See section "Treatment" (Nonpharmacologic Therapy [Interventional Approaches (Antireflux Surgery)]) in chapter for more information.

11. **A.** Patientswith mild, intermittent GERD symptomsless thantwoweeks,are candidates for patient-directed therapy with a non-prescription medication (antacids, H2-receptor antagonist, or proton pump inhibitors). If symptoms do not resolve after the initial treatment period of about 2 weeks, further evaluation is warranted. See section "Treatment" (Pharmacologic Therapy [Patient-Directed Therapy] [Acid Suppression Therapy]) for more information.

12. **D.** Patients with no additional risk factors for osteoporosis should not receive additional calcium supplementation or screening or monitoring of bone mineral density because data is lacking to support these practices. See section "Treatment" (Pharmacologic Therapy [Acid Suppression Therapy (PPI)]) of the chapter for more information.

13. **B.** Gastric acidity plays an important role in the absorption of minerals such as calcium and magnesium, thus leading to low serum concentrations, as well as with vitamin B12 absorption. The change in pH also has a downstream effect on colonic bacteria increasing the risk for *Clostridium difficile* infections. PPIs have not been shown to have a significant effect on potassium homeostasis or Vitamin A absorption. See section "Treatment" (Pharmacologic Therapy [Acid Suppression Therapy (PPI)] of the chapter for more information.

14. **B.** Patient-directed therapy is appropriate when the patient's symptoms are mild and intermittent. Patients with persistent symptoms, more severe symptoms (especially alarm symptoms such as dysphagia, or atypical symptoms (e.g., cough, asthma) will require a standard course of prescription strength acid suppression with a proton pump inhibitor. See section "Treatment" (Pharmacologic Therapy [Patient-Directed Therapy] [Acid Suppression Therapy (PPI)]) of the chapter for more information.

15. **A.** Maintenance therapy is indicated in patients who have symptomatic relapse following discontinuation of acid suppression therapy, especially those with more severe disease. It is also indicated for patients with complications such as Barrett's esophagus or erosive esophagitis. See section "Treatment" (Pharmacologic Therapy [Maintenance Therapy]) of the chapter for more information.