

## Chapter 24: Gastroesophageal Reflux Disease

### INTRODUCTION

- *Gastroesophageal reflux disease* (GERD) is symptoms or complications resulting from refluxed stomach contents into the esophagus, oral cavity (including the larynx), or lungs. Episodic heartburn that is not frequent or painful enough to be bothersome is not included in the definition.

### PATHOPHYSIOLOGY

- In some cases, reflux is associated with defective lower esophageal sphincter (LES) pressure or function. Patients may have decreased LES pressure from spontaneous transient LES relaxations, transient increases in intra-abdominal pressure, or an atonic LES. Some foods and medications decrease LES pressure (**Table 24-1**).
- Problems with other normal mucosal defense mechanisms may contribute to development of GERD, including 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.
- Esophagitis occurs when the esophagus is repeatedly exposed to refluxed gastric contents for prolonged periods. This can progress to erosion of the squamous epithelium of the esophagus (erosive esophagitis).
- Substances that promote esophageal damage upon reflux into the esophagus include gastric acid, pepsin, bile acids, and pancreatic enzymes. Composition and volume of the refluxate and duration of exposure are the primary determinants of the consequences of gastroesophageal reflux.
- An “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. GERD patients are predisposed to upward migration of acid from the acid pocket, which may also be positioned above the diaphragm in patients with hiatal hernia, increasing the risk for acid reflux.
- Reflux and heartburn are common in pregnancy because of hormonal effects on LES tone and increased intra-abdominal pressure from an enlarging uterus.
- Obesity is a risk factor for GERD due to increased intra-abdominal pressure. Transient LES relaxations, an incompetent LES, and impaired esophageal motility have also been attributed to obesity.
- Complications from long-term acid reflux include esophagitis, esophageal strictures, Barrett esophagus, and esophageal adenocarcinoma.

TABLE 24-1

**Foods and Medications That May Worsen GERD Symptoms**

Foods/Beverages	Medications
<b>Decreased lower esophageal sphincter pressure</b>	
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
<b>Direct irritants to the esophageal mucosa</b>	
Spicy foods	Aspirin
Orange juice	Bisphosphonates
Tomato juice	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Coffee	Iron
Tobacco	Quinidine Potassium choride

## CLINICAL PRESENTATION

- *Symptom-based GERD* (with or without esophageal tissue injury) typically presents with heartburn, usually described as a substernal sensation of warmth or burning rising up from the abdomen that may radiate to the neck. It may wax and wane in character and be aggravated by activities that worsen reflux (eg, recumbent position, bending-over, eating a high-fat meal). Other symptoms are water brash (hypersalivation), belching, and regurgitation. Alarm symptoms that may indicate complications include dysphagia, odynophagia, bleeding, and weight loss. The absence of tissue injury or erosions is termed nonerosive reflux disease (NERD).
- *Tissue injury-based GERD* (with or without esophageal symptoms) may present with esophagitis, esophageal strictures, Barrett esophagus, or esophageal carcinoma. Alarm symptoms may also be present.

- Extraesophageal symptoms may include chronic cough, laryngitis, wheezing, and asthma.

## DIAGNOSIS

- Clinical history is sufficient to diagnose GERD in patients with typical symptoms.
- Perform diagnostic tests in patients who do not respond to therapy or who present with alarm symptoms. Endoscopy is preferred for assessing mucosal injury and identifying strictures, Barrett esophagus, and other complications.
- Ambulatory pH monitoring, combined impedance–pH monitoring, high-resolution esophageal pressure topography (HREPT), impedance manometry, and an empiric trial of a proton pump inhibitor (PPI) may be useful in some situations.

## TREATMENT

- Goals of Treatment: The goals are to reduce or eliminate symptoms, decrease frequency and duration of gastroesophageal reflux, promote healing of injured mucosa, and prevent complications.

### General Approach

- Therapy is directed toward decreasing acidity of the refluxate, decreasing the gastric volume available to be refluxed, improving gastric emptying, increasing LES pressure, enhancing esophageal acid clearance, and protecting the esophageal mucosa.
- Treatment is determined by disease severity and includes the following:
  - ✓ Lifestyle changes and patient-directed therapy with **antacids** and/or nonprescription acid suppression therapy (**histamine 2–receptor antagonists [H<sub>2</sub>RAs]** and/or **PPIs**)
  - ✓ Pharmacologic treatment with prescription-strength acid suppression therapy
  - ✓ Antireflux surgery
  - ✓ Endoscopic therapies
- The initial intervention depends in part on the patient’s condition (symptom frequency, degree of esophagitis, and presence of complications). A step-down approach is most often advocated, starting with a PPI instead of an H<sub>2</sub>RA, and then stepping down to the lowest dose of acid suppression needed to control symptoms (**Table 24-2**).
- Patient-directed therapy (self-treatment with nonprescription medication) is appropriate for mild, intermittent symptoms. Patients with continuous symptoms for longer than 2 weeks should seek medical attention; such patients are generally started on empiric acid-suppression therapy. Patients not responding satisfactorily or those with alarm symptoms (eg, dysphagia) should undergo endoscopy.

TABLE 24-2

#### Therapeutics Approach to GERD in Adults

Recommended Treatment Regimen	Brand Name	Oral Dose	Comments
Intermittent, mild heartburn (individualized lifestyle modifications + patient-directed therapy with antacids and/or nonprescription H <sub>2</sub> RAs or nonprescription PPI)			

Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
<b>Patient-directed therapy with antacids (≥12 years old)</b>			
Magnesium hydroxide/Aluminum hydroxide with simethicone	Maalox	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	Gaviscon	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	Tums	500 mg, 2–4 tablets as needed	
<b>Patient-directed therapy with nonprescription H<sub>2</sub>RAs (up to twice daily) (≥12 years old)</b>			
Cimetidine Famotidine Nizatidine Ranitidine	Tagamet HB Pepcid AC Axid AR Zantac	200 mg 10–20 mg 75 mg 75–150 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention
<b>Patient-directed therapy (&gt;18 years old) with nonprescription PPIs (taken once daily)</b>			
Esomeprazole Lansoprazole Omeprazole Omeprazole/sodium bicarbonate	Nexium 24HR Prevacid 24HR Prilosec OTC Zegerid OTC	20 mg 15 mg 20 mg 20 mg/1100 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention
<b>Symptomatic relief of GERD (individualized lifestyle modifications + prescription-strength H<sub>2</sub>RAs or prescription-strength PPIs)</b>			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
<b>Prescription-strength H<sub>2</sub>RAs (for 6–12 weeks)</b>			
Cimetidine (off-label use) Famotidine Nizatidine	Tagamet Pepcid Axid Zantac	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

Ranitidine		20 mg twice daily 150 mg twice daily 150 mg twice daily	
<b>Prescription-strength PPIs (for 4–8 weeks)</b>			
Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Omeprazole/Sodium bicarbonate Pantoprazole (off-label use) Rabeprazole	Dexilant Nexium Prevacid Prilosec Zegerid Protonix Aciphex	30 mg once daily for 4 weeks 20–40 mg once daily 15 mg once daily 20 mg once daily 20 mg once daily 20 mg once daily	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
<b>Healing of erosive esophagitis or treatment of patients with moderate-to-severe symptoms or complications (individualized lifestyle modifications + high-dose H<sub>2</sub>RAs or PPIs or antireflux surgery)</b>			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
<b>PPIs (up to twice daily for up to 8 weeks)</b>			
Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Rabeprazole Pantoprazole	Dexilant Nexium Prevacid Prilosec Aciphex Protonix	60 mg daily 20–40 mg daily 30 mg once or twice daily 20 mg once or twice daily 20 mg once or twice daily 40 mg once or twice 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 present Patients not responding to pharmacologic therapy, including those with persistent extraesophageal symptoms, should be evaluated via manometry and/or ambulatory reflux monitoring
<b>High-dose H<sub>2</sub>RAs (for 8–12 weeks)</b>			
Cimetidine	Tagamet	400 mg four times daily or 800 mg twice daily	If high-dose H <sub>2</sub> RA needed, may consider using PPI to lower cost, increase convenience, and increase tolerability
Famotidine	Pepcid	20–40 mg twice daily	Four times daily H <sub>2</sub> RA is considered off-label use for nizatidine
Nizatidine	Aciphex	150 mg two to four times daily	

Ranitidine	Zantac	150 mg four times daily	
<b>Interventional therapy</b>			
Antireflux surgery			
Bariatric surgery			
Endoscopic therapies			

H<sub>2</sub> RA, histamine<sub>2</sub> -receptor antagonist; PPI, proton pump inhibitor.

## Nonpharmacologic Therapy

- Potential lifestyle changes depending on the patient situation:
  - ✓ Elevate head of the bed by placing 6- to 8-in blocks under the headposts. Sleep on a foam wedge.
  - ✓ Weight reduction for overweight or obese patients.
  - ✓ Avoid foods that decrease LES pressure (eg, fats, chocolate).
  - ✓ Include protein-rich meals to augment LES pressure.
  - ✓ Avoid foods with irritant effects on the esophageal mucosa (eg, citrus juices, coffee, pepper).
  - ✓ Eat small meals and avoid eating immediately prior to sleeping (within 3 hours if possible).
  - ✓ Stop smoking.
  - ✓ Avoid alcohol.
  - ✓ Avoid tight-fitting clothes.
  - ✓ For mandatory medications that irritate the esophageal mucosa, take in the upright position with plenty of liquid or food (if appropriate).
- Antireflux surgery (eg, laparoscopic Nissen fundoplication) should be considered when long-term pharmacotherapy is undesirable or when patients have complications. Bariatric surgery, specifically Roux-en-Y gastric bypass, should be considered in obese patients (BMI >35 kg/m<sup>2</sup>) contemplating surgery.
- Two endoscopic therapies are: (1) radiofrequency ablation (for managing Barrett esophagus primarily when dysplasia is present), and (2) transoral incisionless fundoplication (for select patients with chronic GERD).
- Magnetic sphincter augmentation can improve lower esophageal resistance and reduce GERD symptoms. Five-year results showed long-term reduction in esophageal acid and symptom improvement with minimal complications.

## Pharmacologic Therapy

### Antacids and Antacid-Alginic Acid Products

- Antacids provide immediate symptomatic relief for mild GERD and are often used concurrently with acid suppression therapies. Patients who require frequent use for chronic symptoms should receive prescription-strength acid suppression therapy instead.
- Some antacid products are combined with alginic acid, which is not a potent acid-neutralizing agent and does not enhance LES pressure, but it

forms a viscous solution that floats on the surface of gastric contents. This serves as a protective barrier for the esophagus against reflux of gastric contents and reduces frequency of reflux episodes. The combination product may be superior to antacids alone in relieving GERD symptoms, but efficacy data indicating endoscopic healing are lacking.

- Antacids have a short duration, which necessitates frequent administration throughout the day to provide continuous acid neutralization. Taking antacids after meals can increase duration from approximately 1 hour to 3 hours; however, nighttime acid suppression cannot be maintained with bedtime doses. Antacids may cause diarrhea or constipation depending on the magnesium or aluminum content. These agents have significant drug interactions with [tetracycline](#), [ferrous sulfate](#), [isoniazid](#), sulfonyleureas, and quinolone antibiotics.

## Proton Pump Inhibitors

- [Dexlansoprazole](#), [esomeprazole](#), [lansoprazole](#), [omeprazole](#), [pantoprazole](#), and [rabeprazole](#) block gastric acid secretion by inhibiting hydrogen potassium adenosine triphosphatase in gastric parietal cells, resulting in profound and long-lasting antisecretory effects.
- PPIs provide more rapid symptom relief and higher healing rates than H<sub>2</sub>RAs in patients with moderate-to-severe GERD and should be given empirically to patients with troublesome symptoms. Twice-daily use is indicated in patients not responding to standard once-daily therapy.
- Adverse effects include headache, diarrhea, nausea, and abdominal pain. Community-acquired pneumonia has occurred with short-term use. Potential long-term adverse effects include enteric infections, vitamin B<sub>12</sub> deficiency, hypomagnesemia, and bone fractures. PPIs can decrease the absorption of [ketoconazole](#) and [itraconazole](#), which require an acidic environment for absorption. Although some PPIs (especially [omeprazole](#)) inhibit cytochrome P450 2C19 and may reduce conversion of [clopidogrel](#) to its active metabolite, the only prospective randomized clinical trial conducted to date found no increased rate of clinical events in patients given [clopidogrel](#) plus [omeprazole](#).
- PPIs degrade in acidic environments and are therefore formulated in delayed-release capsules or tablets. [Dexlansoprazole](#), [esomeprazole](#), [lansoprazole](#), and [omeprazole](#) contain enteric-coated (pH-sensitive) granules in capsules. For patients unable to swallow the capsules, the contents can be mixed in applesauce or orange juice. In patients with nasogastric tubes, the contents 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, and [lansoprazole](#) is available as a delayed-release, orally disintegrating tablet. [Rabeprazole](#) is available in a capsule sprinkle that can be opened and placed in a small amount of soft food such as applesauce. Patients taking delayed-release tablets of [pantoprazole](#) or [rabeprazole](#) should be instructed not to crush, chew, or split them. [Dexlansoprazole](#) is available in a dual delayed-release capsule, with the first release occurring 1–2 hours after the dose, and the second release occurring 4–5 hours after the dose.
- [Zegerid](#)<sup>®</sup> is a combination product containing [omeprazole](#) 20 or 40 mg with 1100 mg [sodium bicarbonate](#) in immediate-release oral capsules and powder for oral suspension. It should be taken on an empty stomach at least 1 hour before a meal. The capsules should be swallowed whole and not opened, sprinkled on food, or administered via nasogastric tube. The powder for oral suspension offers an alternative to delayed-release capsules or IV formulation in adults with nasogastric tubes.
- [Lansoprazole](#), [esomeprazole](#), and [pantoprazole](#) are available in IV formulations for patients who cannot take oral medications, but they are not more effective than oral preparations and are significantly more expensive.
- Patients should take oral PPIs in the morning 30–60 minutes before breakfast or their largest meal of the day to maximize efficacy, because these agents inhibit only actively secreting proton pumps. [Dexlansoprazole](#) can be taken without regard to meals. If dosed twice daily, the second PPI dose should be taken approximately 10–12 hours after the morning dose and prior to a meal or snack.

## Histamine 2–Receptor Antagonists

- [Cimetidine](#), [ranitidine](#), [famotidine](#), and [nizatidine](#) in divided doses are effective for treating mild-to-moderate GERD. Low-dose nonprescription H<sub>2</sub>RAs or standard doses given twice daily may be beneficial for symptomatic relief of mild GERD. Patients not responding to standard doses may be hypersecretors of gastric acid and require higher doses ([Table 24-2](#)). However, when standard doses of H<sub>2</sub>RAs do not adequately relieve symptoms, it is more cost-effective and clinically effective to switch to a PPI. The efficacy of H<sub>2</sub>RAs for GERD treatment is highly variable and frequently less than desired. Prolonged courses are frequently required.

- The most common adverse effects include headache, fatigue, dizziness, and either constipation or diarrhea. **Cimetidine** may inhibit the metabolism of **theophylline**, **warfarin**, **phenytoin**, **nifedipine**, and **propranolol**, among other drugs.
- Because all H<sub>2</sub>RAs are equally effective, selection of the specific agent should be based on differences in pharmacokinetics, safety profile, and cost.

### Promotility Agents

- Promotility agents may be useful adjuncts to acid-suppression therapy in patients with a known motility defect (eg, LES incompetence, decreased esophageal clearance, delayed gastric emptying). However, these agents are not as effective as acid suppression therapy and have undesirable adverse effects.
- **Metoclopramide**, a **dopamine** antagonist, increases LES pressure in a dose-related manner and accelerates gastric emptying. However, it does not improve esophageal clearance. **Metoclopramide** provides symptomatic improvement for some patients, but evidence supporting endoscopic healing is lacking. Common adverse reactions include somnolence, nervousness, fatigue, dizziness, weakness, depression, diarrhea, and rash. In addition, extrapyramidal effects, tardive dyskinesia, and other CNS effects limit its usefulness.
- **Bethanechol** has limited value because of side effects (eg, urinary retention, abdominal discomfort, nausea, flushing). It is not routinely recommended for treatment of GERD.

### Mucosal Protectants

- **Sucralfate** is a nonabsorbable aluminum salt of **sucrose** octasulfate. It has limited value for treatment of GERD but may be useful for management of radiation esophagitis and bile or nonacid reflux GERD.

### Combination Therapy

- Combination therapy with an acid-suppressing agent and a promotility agent or mucosal protectant seems logical, but data supporting such therapy are limited. This approach is not recommended unless a patient has GERD with motor dysfunction. Using the omeprazole-sodium bicarbonate immediate-release product in addition to once daily PPI therapy offers an alternative for nocturnal GERD symptoms.

### Maintenance Therapy

- Many patients with GERD relapse after medication is withdrawn, so maintenance treatment may be required. Consider long-term therapy to prevent complications and worsening of esophageal function in patients who have symptomatic relapse after discontinuation of therapy or dosage reduction, including patients with Barrett esophagus, strictures, or erosive esophagitis.
- Most patients require standard doses to prevent relapses. PPIs are the drugs of choice for maintenance treatment of moderate-to-severe esophagitis or symptoms. Usual once-daily doses are **omeprazole** 20 mg, **lansoprazole** 30 mg, **rabeprazole** 20 mg, or **esomeprazole** 20 mg. Low doses of a PPI or alternate-day regimens may be effective in some patients with milder symptoms. H<sub>2</sub>RAs may be effective maintenance therapy in patients with mild disease.
- “On-demand” maintenance therapy, by which patients take their PPIs only when they have symptoms, may be effective for patients with endoscopy-negative GERD.

## EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor frequency and severity of GERD symptoms, and educate patients on symptoms that suggest presence of complications requiring immediate medical attention, such as dysphagia. Evaluate patients with persistent symptoms for presence of strictures or other complications.
- Monitor patients for adverse drug effects and the presence of extraesophageal symptoms such as laryngitis, asthma, or chest pain. These symptoms require further diagnostic evaluation.

---

See Chapter 49, Gastroesophageal Reflux Disease, authored by Dianne B. May, Michael Thiman, and Satish S.C. Rao, for a more detailed discussion of this topic.