Pharmacotherapy 2

Gastroesophageal Reflux Disease (GERD)

Dr Enaam M. Al Momany
Faculty of Pharmaceutical Sciences
Department of Clinical Pharmacy and Pharmacy Practice

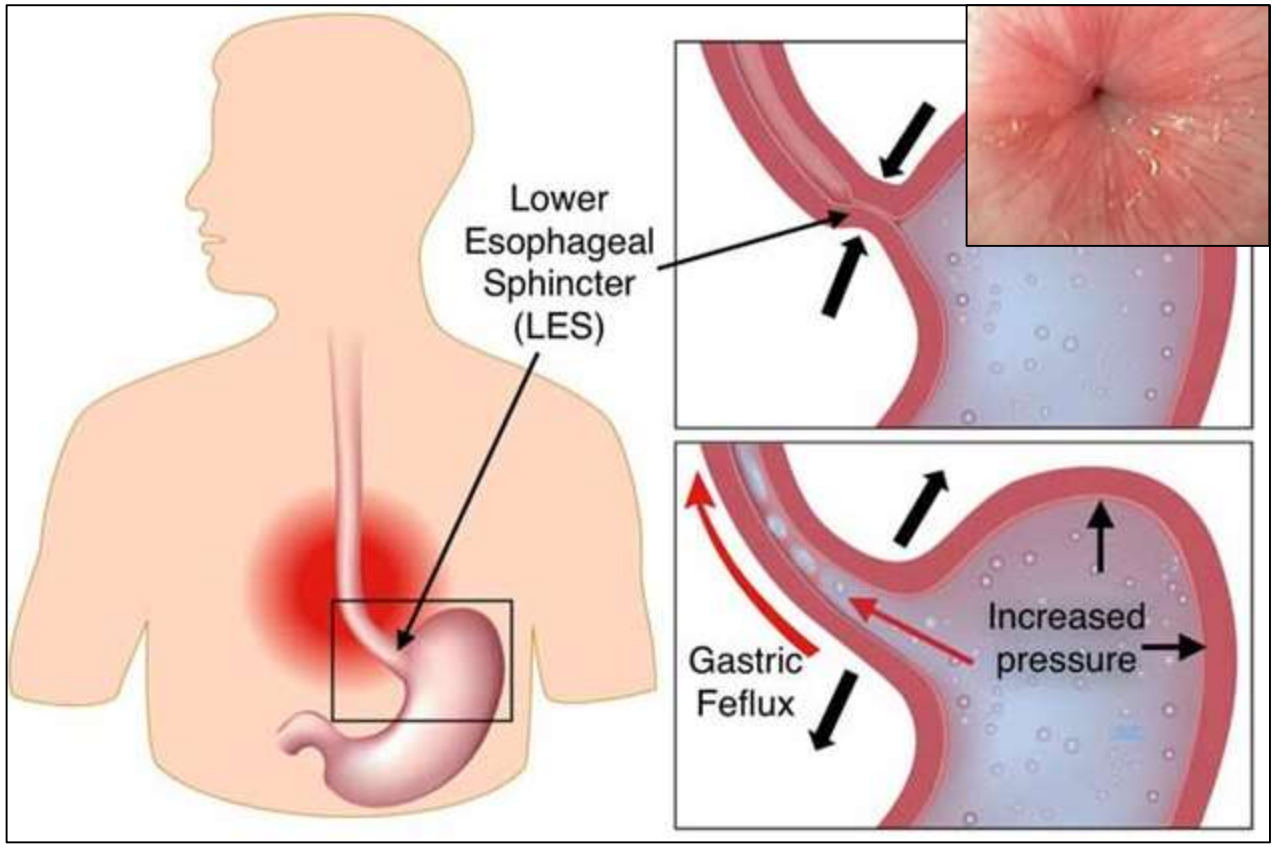
Topic Outline

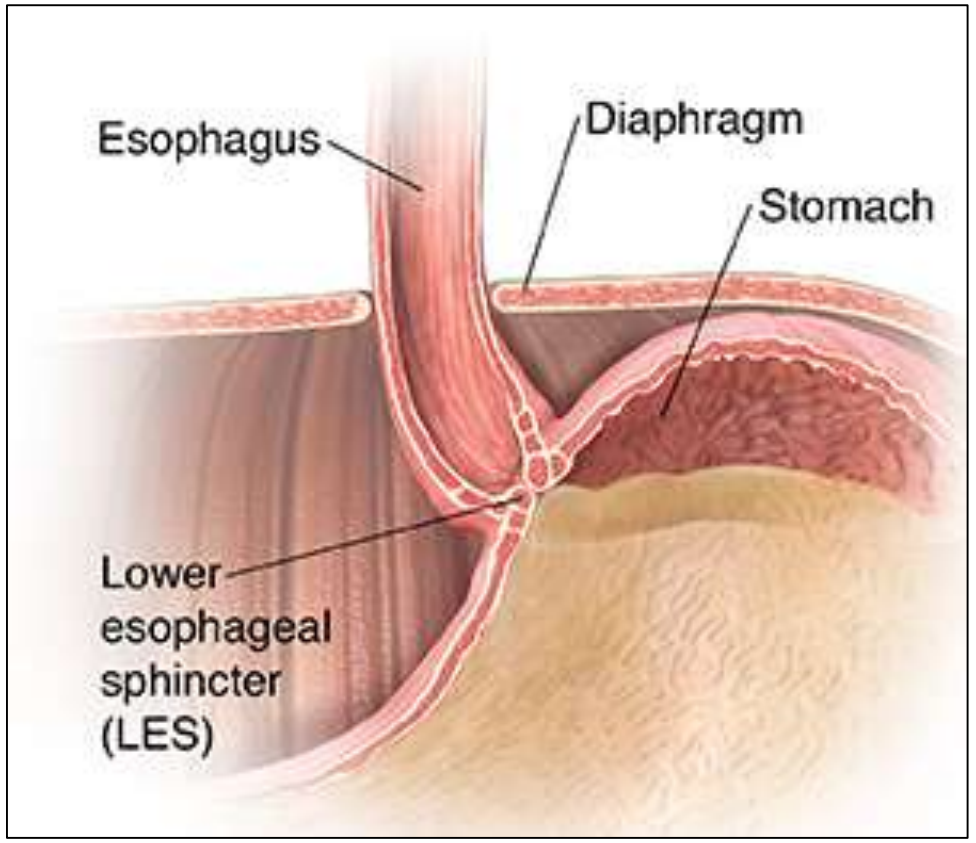
- General Principles
- Diagnosis (Clinical Presentations, Diagnostic Testing)
- Treatment (Nonpharmacologic Tx, Medications, Surgical Management)
- Complications

Gastroesophageal Reflux Disease (GERD)

General Principles

GERD is defined as symptoms and/ or complications resulting from reflux of gastric contents into the esophagus and more proximal structures.





Diagnosis

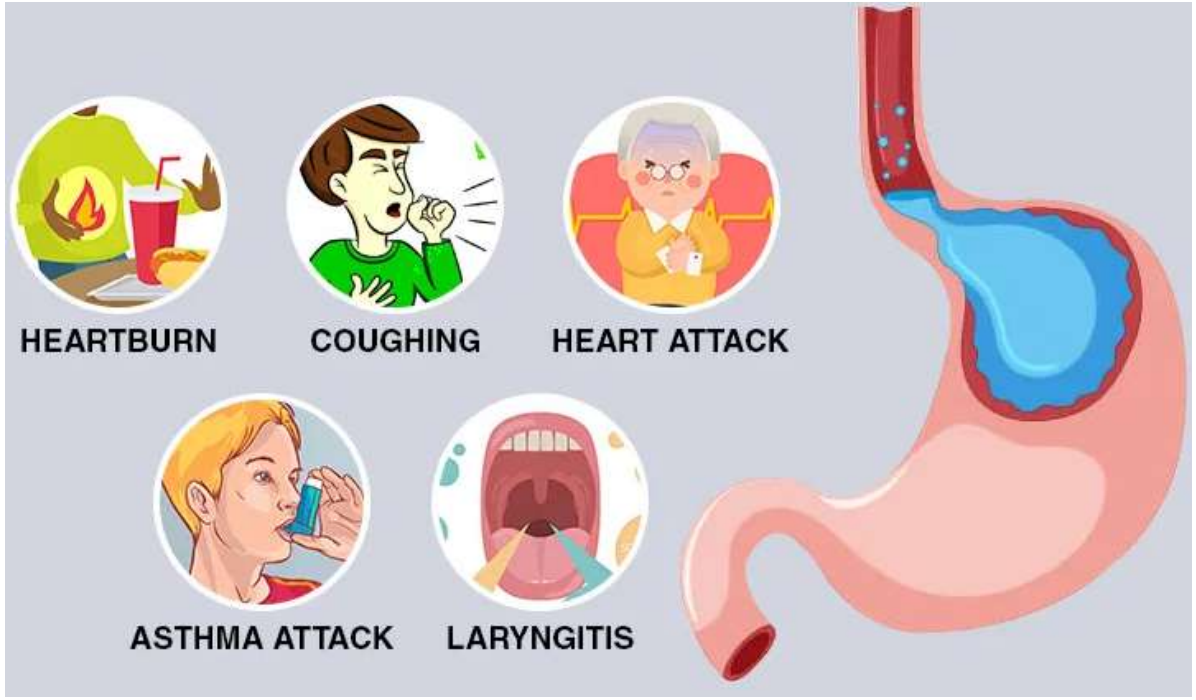
✓ Clinical Presentation:

- Typical esophageal symptoms include heartburn and regurgitation

- GERD can also present as chest pain, where an important priority is to exclude a cardiac source before initiating GI evaluation.

- Extraesophageal manifestations of GERD: cough, laryngitis, asthma, and dental erosions

- Symptom response to a therapeutic trial of PPIs can be diagnostic, but a negative response does not exclude GERD.



CLINICAL PRESENTATION

GERD[1,17,22,23]

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):

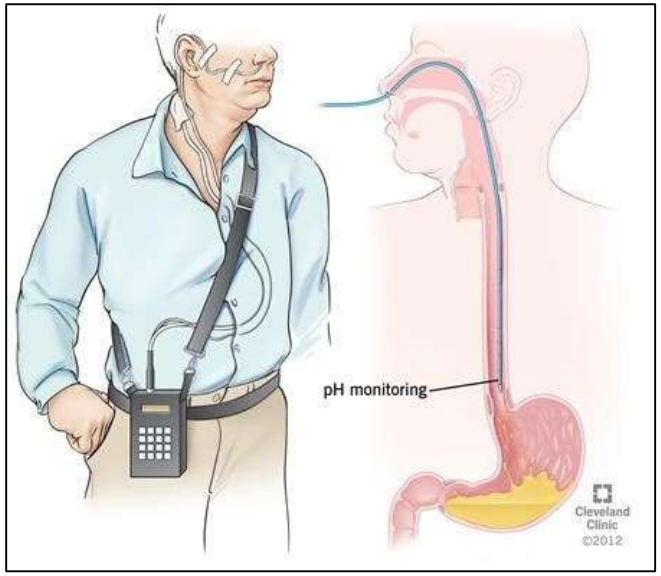
- Esophagitis
- Strictures
- Barrett's esophagus
- Esophageal adenocarcinoma

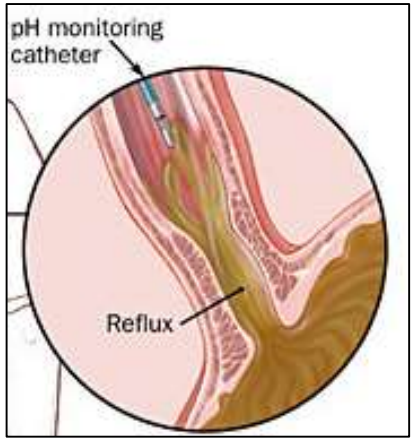
Extraesophageal GERD Syndromes

- 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 Testing:

- Endoscopy with biopsies
- Ambulatory pH monitoring
- Esophageal manometry





Treatment

✓ Nonpharmacologic Treatment with Lifestyle Modifications:

- Elevate the head end of the bed (increases esophageal clearance). Use 15-20 cm blocks under the head side of the bed

- Weight reduction (reduces symptoms) in obese patients

- Avoid foods that may decrease LES pressure or increase transient LES relaxation (fats, chocolate, alcohol, peppermint, and spearmint)

- Include protein-rich meals in diet

- 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)
  - Stop smoking
  - Avoid alcohol
  - 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, NSAIDs)

✓ Medications

- Intermittent or prophylactic OTC antacids, H2RAs, and PPIs are effective with mild or intermittent symptoms.

- PPIs are more effective than standard-dose H2RA and placebo in symptom relief and endoscopic healing of GERD.

- Modest gain is achieved by doubling the PPI dose in severe esophagitis or persistent symptoms.
- Continuous long-term PPI therapy is effective in maintaining remission of GERD symptoms, but the dose should be decreased after 8– 12 weeks to the lowest dose that achieves symptom relief.
- Abdominal pain, headache, and diarrhea are common side effects.
- Bone demineralization, enteric infections, CAP, and reduced circulating levels of vitamin B12 are reported in observational studies, but conclusive cause-and-effect data are lacking, and benefits of PPI therapy continue to outweigh risks.

TABLE 49-1 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 (NSAIDs)
Coffee	Iron
Tobacco	Quinidine
	Potassium chloride

TABLE 49-2 Evidence-Based Treatment Recommendations for GERD in Adults[1,24]

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 nighttime symptoms, variable schedules, and/or sleep disturbances who are partial responders to PPI therapy.	Low, Strong
• In patients with typical GERD symptoms who also have extraesophageal symptoms, a PPI trial is recommended.	Low, Strong
• Optimization of proton pump inhibitor 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 generally recommended in nonpregnant GERD patients.	Moderate, Conditional
Maintenance Therapy	
• Maintenance therapy is recommended for (1) patients with continued symptoms after PPI discontinuation; (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
• H2-receptor antagonists may be used as maintenance therapy in patients without erosive disease when the goal is heartburn relief.	Moderate, Conditional

Surgery	
• Surgery is a long-term treatment option in GERD patients.	High, Strong
• Surgery is not generally recommended in PPI nonresponders.	High, Strong
• Surgery is not generally 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

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.

TABLE 49-3 Therapeutic 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_2RAs *or* nonprescription PPIs)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
Patient-directed therapy with antacids (≥12 years old)			
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	
Patient-directed therapy with nonprescription H2-receptor antagonists (up to twice daily) (≥12 years old)			
Cimetidine	Tagamet HB®	200 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention
Famotidine	Pepcid AC®	10-20 mg	
Nizatidine	Axid AR®	75 mg	
Ranitidine	Zantac®	75-150 mg	

Patient-directed therapy (>18 years old) with nonprescription proton pump inhibitors (taken once daily)			
Esomeprazole	Nexium® 24HR	20 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention
Lansoprazole	Prevacid® 24HR	15 mg	
Omeprazole	Prilosec OTC®	20 mg	
Omeprazole/sodium bicarbonate	Zegerid OTC®	20 mg/1,100 mg	
Symptomatic relief of GERD (individualized lifestyle modifications + prescription-strength H2-receptor antagonists *or* prescription-strength proton pump inhibitors)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
Prescription-strength H2RAs (for 6-12 weeks)			
Cimetidine (off-label use)	Tagamet®	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	Pepcid®	20 mg twice daily	
Nizatidine	Axid®	150 mg twice daily	
Ranitidine	Zantac®	150 mg twice daily	
Prescription-strength PPIs (for 4-8 weeks)			
Dexlansoprazole	Dexilant®	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	Nexium®	20-40 mg once daily	
Lansoprazole	Prevacid®	15 mg once daily	
Omeprazole	Prilosec®	20 mg once daily	
Omeprazole/sodium bicarbonate	Zegerid®	20 mg once daily	
Pantoprazole (Off-label use)	Protonix®	40 mg once daily	
Rabeprazole	Aciphex®	20 mg once daily	
Healing of erosive esophagitis or treatment of patients with moderate-to-severe symptoms or complications (individualized lifestyle modifications + high-dose H2-receptor antagonists *or* proton pump inhibitors *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	Dexilant®	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 present • Patients not responding to pharmacologic therapy, including those with persistent extraesophageal symptoms, should be evaluated via manometry and/or ambulatory reflux monitoring
Esomeprazole	Nexium®	20-40 mg daily	
Lansoprazole	Prevacid®	30 mg once or twice daily	
Omeprazole	Prilosec®	20 mg once or twice daily	
Rabeprazole	Aciphex®	20 mg once or twice daily	
Pantoprazole	Protonix®	40 mg once or twice daily	

High-dose H2-receptor antagonists (for 8-12 weeks)			
Cimetidine	Tagamet®	400 mg four times daily or 800 mg twice daily	Note: If high-dose H_2RA needed, may consider using proton pump inhibitor to lower cost, increase convenience, and increase tolerability Note: Four times daily H_2RA is considered off-label use for Nizatidine
Famotidine	Pepcid®	20-40 mg twice daily	
Nizatidine	Aciphex®	150 mg two to four times daily	
Ranitidine	Zantac®	150 mg four times daily	
Interventional therapy			
Antireflux surgery Bariatric surgery Endoscopic therapies			

TABLE 49-5 Drug Monitoring[37,41–43]

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
H2-Receptor Antagonists			
• Cimetidine • Famotidine • Nizatidine • Ranitidine	• Headache, somnolence, fatigue, dizziness, and either constipation or diarrhea	• Monitor for CNS effects, especially in the elderly • Monitor vitamin B_{12} serum concentrations in those on chronic, long-term therapy or in those on higher doses	• 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 B_{12} 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, somnolence, diarrhea, constipation, flatulence, abdominal pain, and nausea

Other important adverse effects:

- Enteric infections (*C. difficile* infections)
- Increased risk of pneumonia

Long-term adverse effects:

- Hypomagnesemia
- Bone fractures
- Vitamin B_{12} deficiency

- 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 vitamin B_{12} serum concentration with long-term use

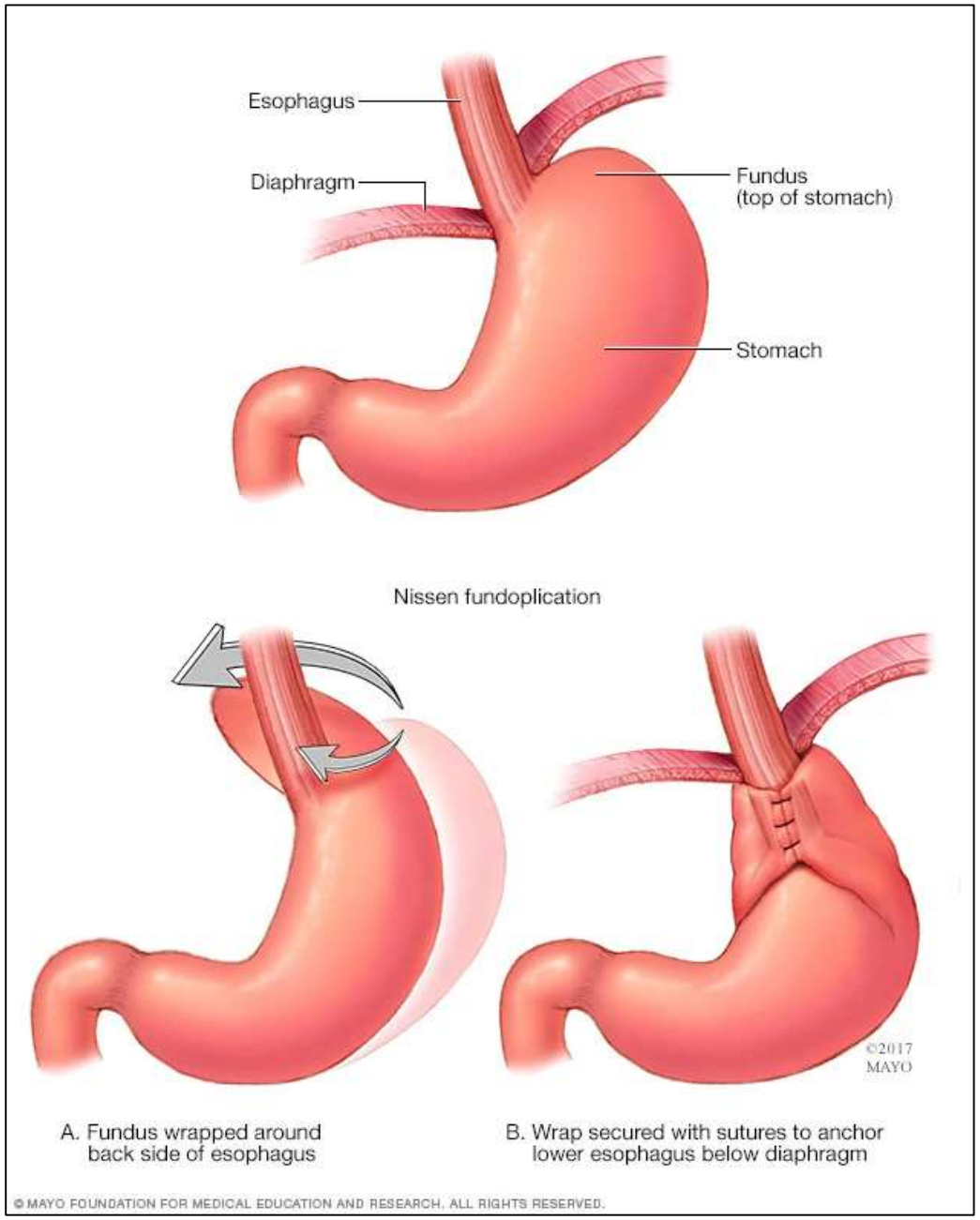
- Acid suppression may result in loss of host defense against ingested spores and bacteria permitting a higher burden of exposure
- Hypomagnesemia is uncommon but can be life-threatening; has been seen as soon as 3 months after starting therapy but more likely in those on PPIs greater than 1 year
- May 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, $\geq$1 year) Patients with known osteoporosis can remain on proton pump inhibitor
- PPIs may inhibit secretion of intrinsic factor, which potentially can lead to vitamin B_{12} deficiency; this is not common and usually associated with use for >3 years
- May increase risk of community-acquired pneumonia, particularly within the first 30 days of therapy

✓ Surgical Management

- Indications for surgical fundoplication include:
  - ➢ the need for continuous PPIs
  - ➢ noncompliance, or intolerance to medical therapy in patients who are good surgical candidates
  - ➢ ongoing nonacid reflux despite adequate medical therapy
  - ➢ patient preference for surgery

- When symptoms are controlled on PPI therapy, medical therapy and fundoplication are equally effective.

- Although fundoplication could provide better symptom control and quality of life in the short term, new postoperative symptoms and surgical failure can also occur.



Complications

- ✓ Esophageal erosion and ulceration (esophagitis) can rarely lead to overt bleeding and IDA.
- ✓ Strictures can form when esophagitis heals, leading to dysphagia. Endoscopic dilation and maintenance PPI therapy typically resolve dysphagia from strictures.
- ✓ Barrett esophagus (BE) is a reflux-triggered change from normal squamous esophageal epithelium to specialized intestinal metaplasia and carries a 0.5% per year risk of progression to esophageal adenocarcinoma. Endoscopic screening for BE should be considered for patients with GERD who are at high risk (long duration of GERD symptoms, ≥ 50 years of age, male gender, Caucasian).