Pharmacotherapy 2

Gastroesophageal Reflux Disease (GERD)

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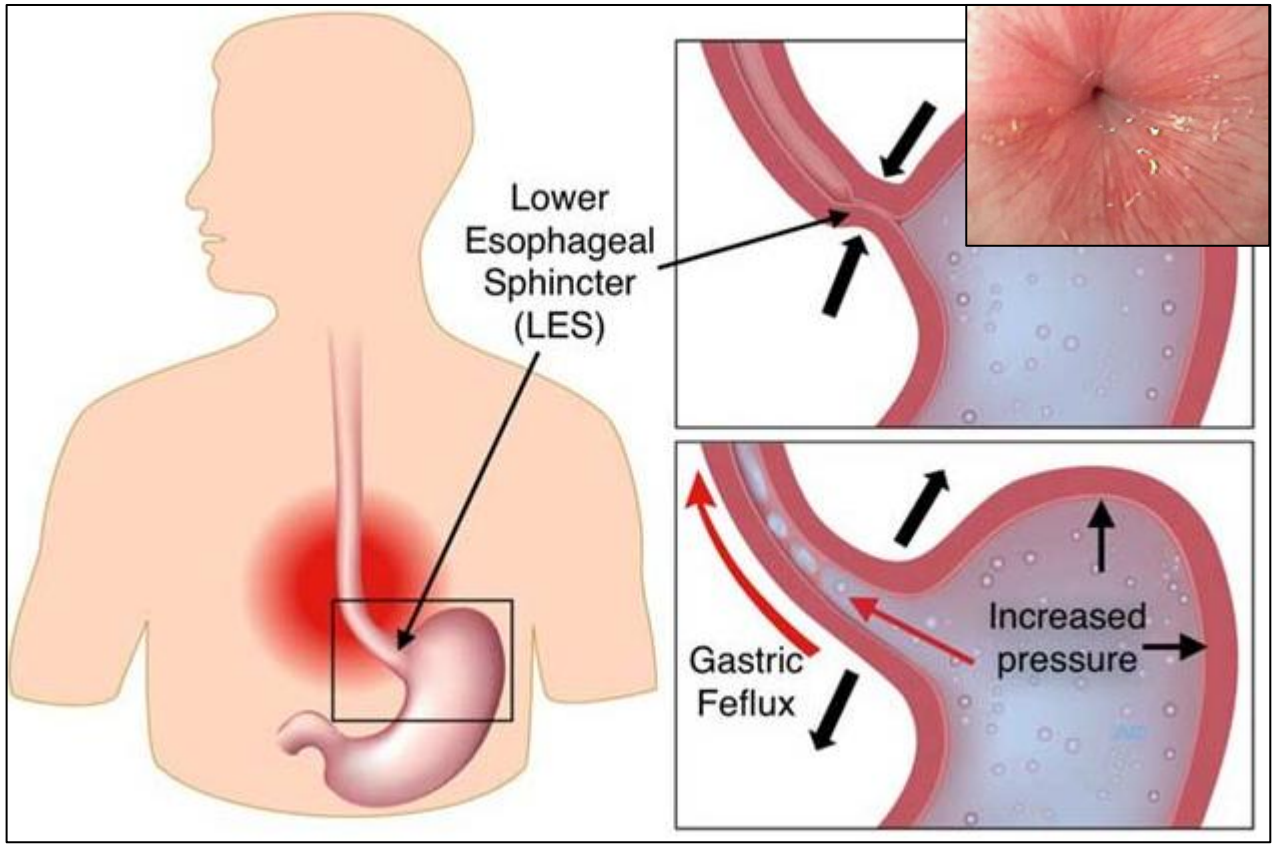
Topic Outline

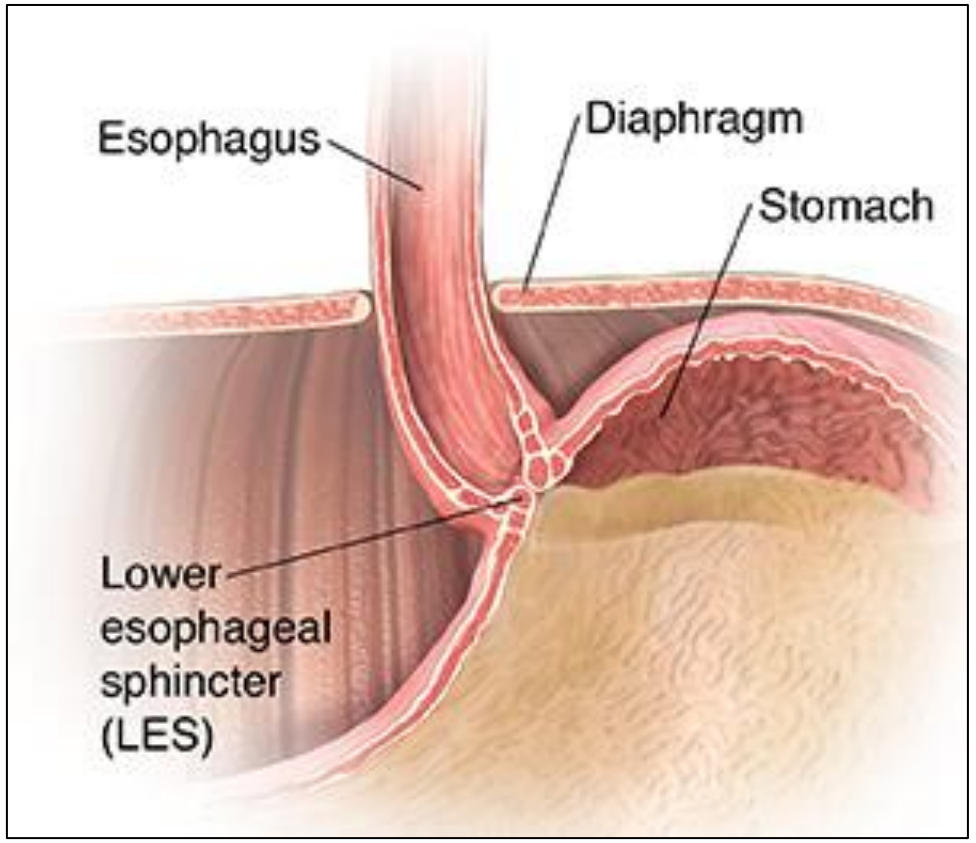
- General Principles
- Diagnosis (Clinical Presentations, Diagnostic Testing)
- Treatment (Nonpharmacologic Tx, Medications, Surgical Management)
- Complications

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

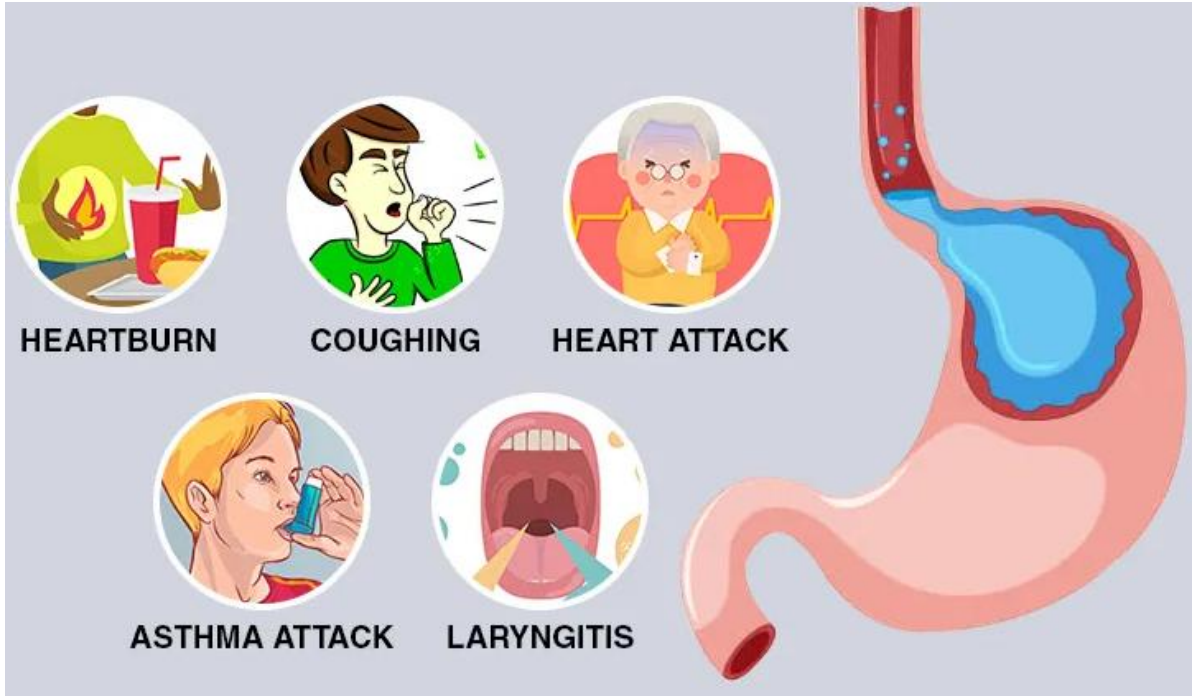
✓ Clinical Presentation:

- 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):

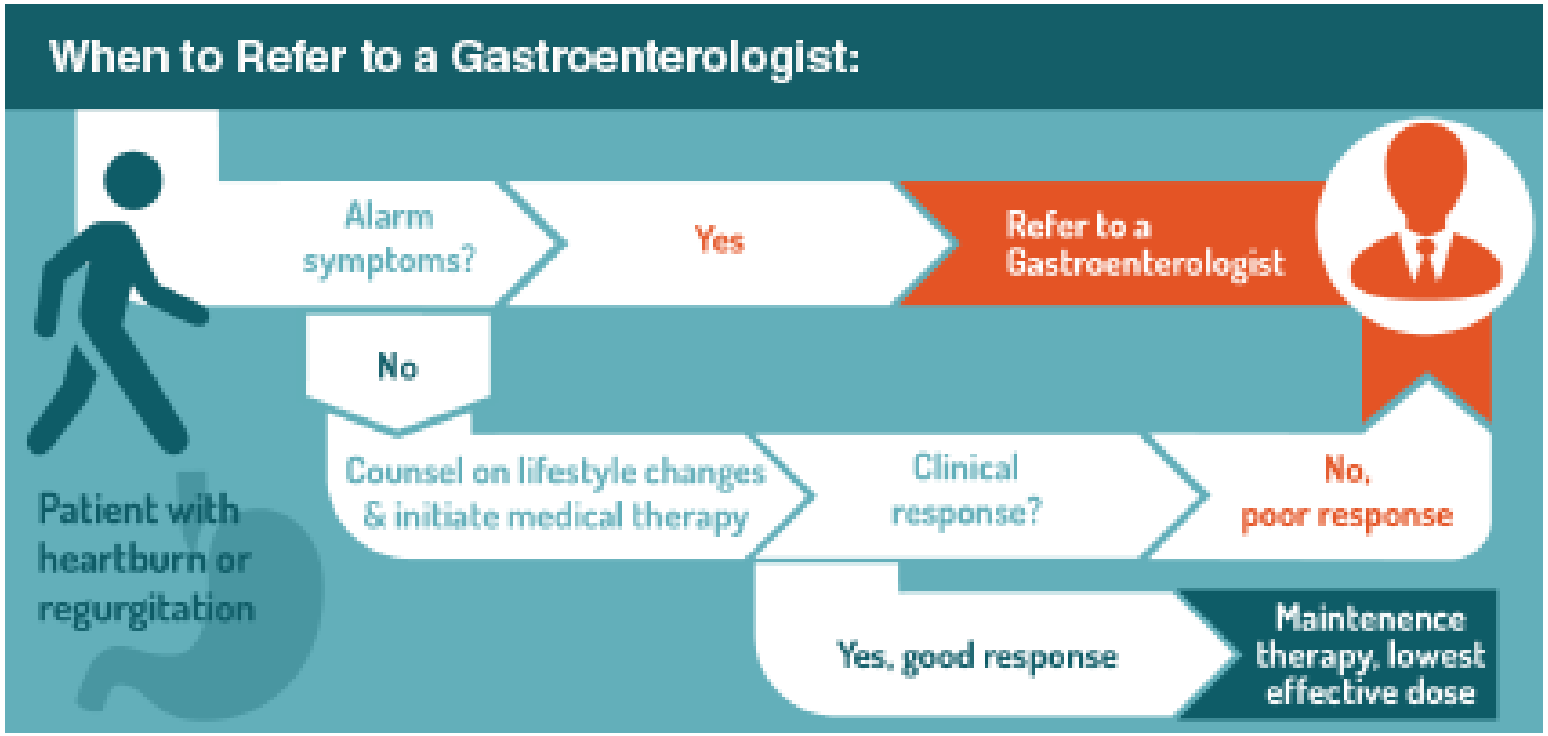
- Esophagitis
- Strictures
- Barrett's esophagus
- Esophageal adenocarcinoma

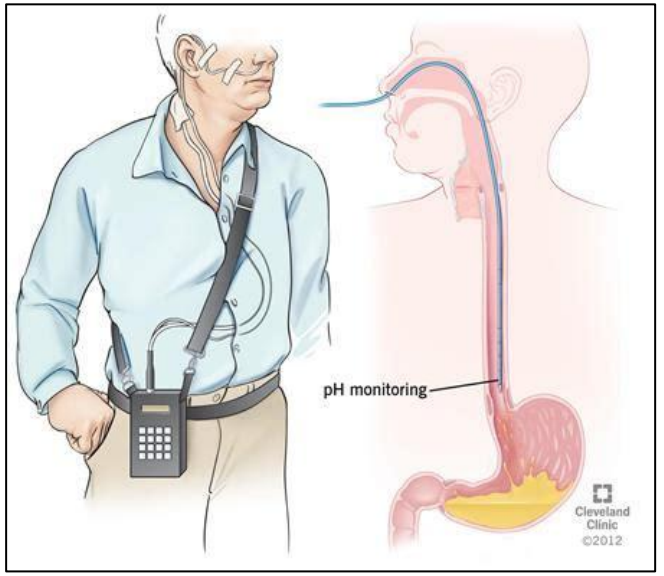
Extraesophageal GERD Syndromes

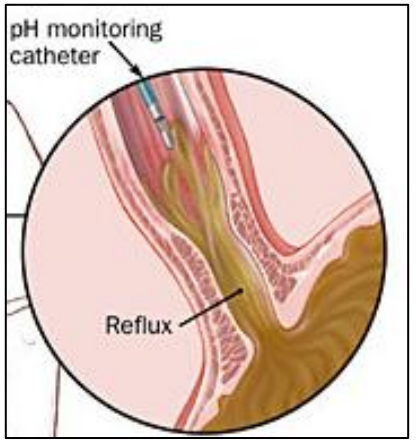
- These symptoms have an association with GERD, but causality should only be considered if a concomitant esophageal GERD syndrome is also present):
- Chronic cough
- Laryngitis
- Wheezing
- Asthma (~50% with asthma have GERD)

✓ Diagnostic Testing:

- Endoscopy with biopsies
- Ambulatory pH monitoring
- Esophageal manometry

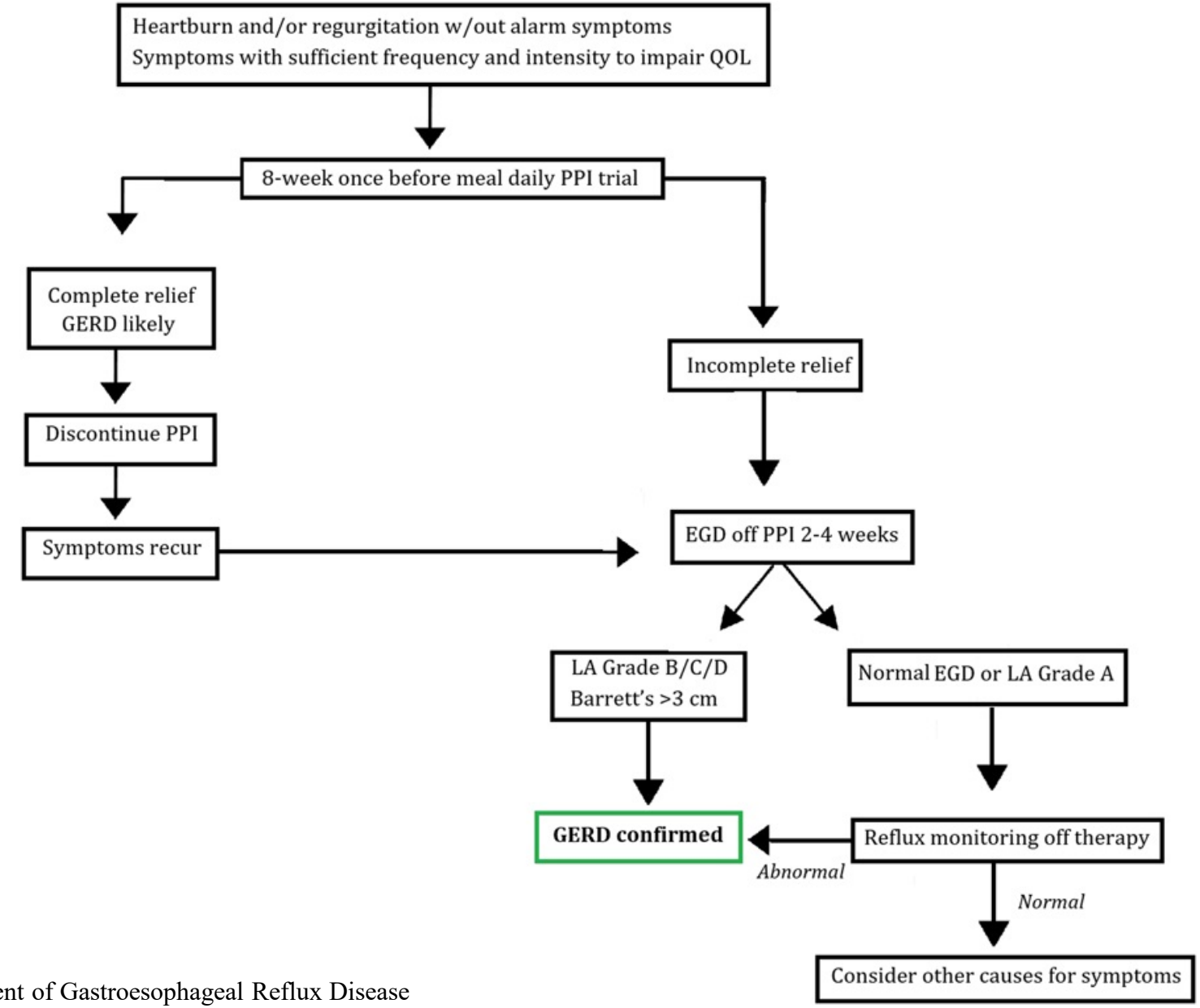






Diagnosis of GERD.

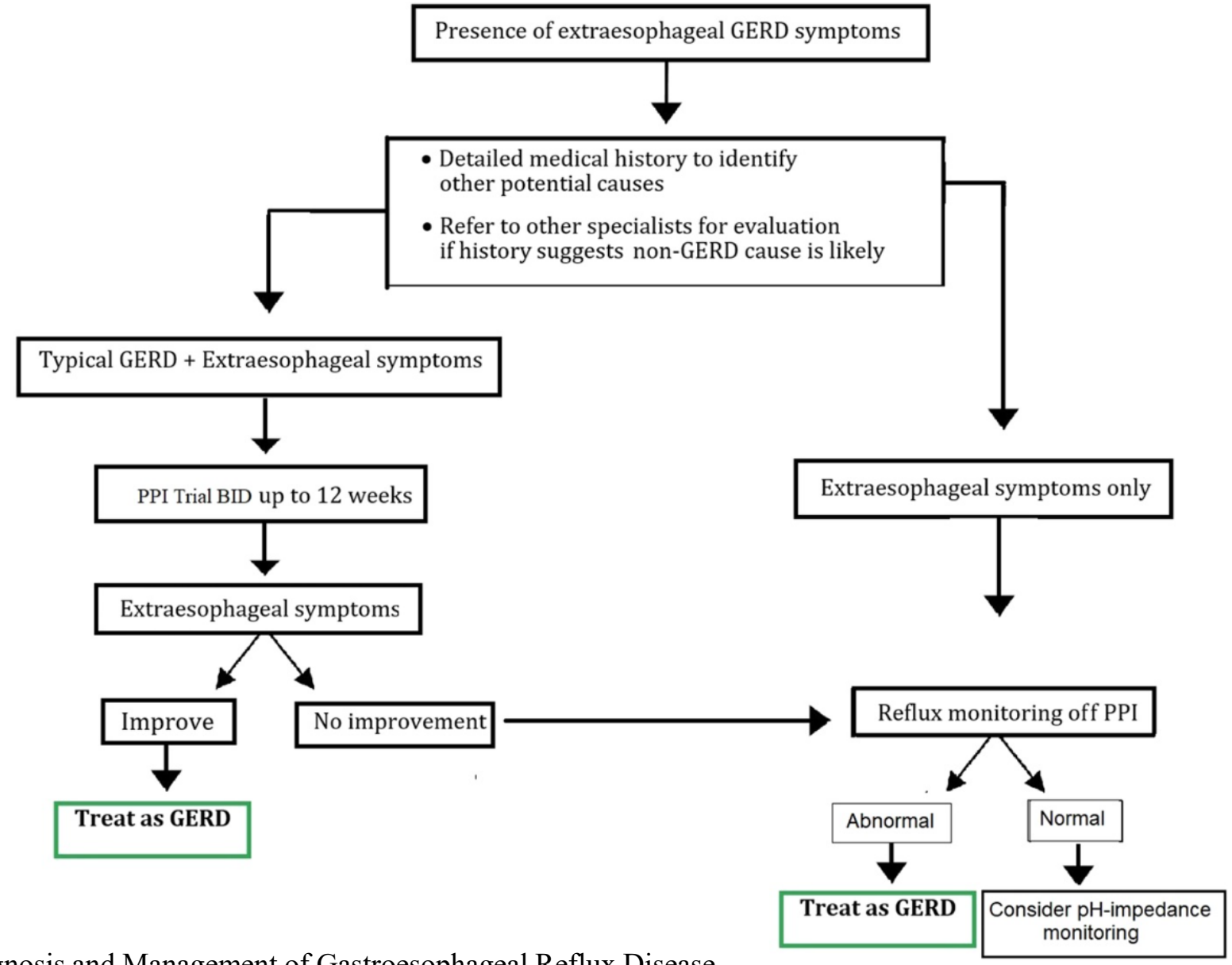
EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; LA, Los Angeles; PPI, proton pump inhibitor; QOL, quality of life.



Source: ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease
Official journal of the American College of Gastroenterology | ACG117(1):27-56, January 2022.

Diagnostic algorithm for extraesophageal GERD symptoms.

BID, twice-daily; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.



Source: ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease Official journal of the American College of Gastroenterology | ACG117(1):27-56, January 2022.

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 3. Recommendations based on results of a review of studies involving lifestyle modifications

Lifestyle modification	Strength of scientific evidence	Pathophysiologically conclusive?	Recommendable?
Avoid fatty meals	Equivocal	Equivocal	Yes
Avoid carbonated beverages	Moderate	Yes	Yes
Select decaffeinated beverages	Equivocal	Equivocal	Not generally
Avoid citrus	Weak	Yes	Yes, if citrus triggers symptoms
Eat smaller meals	Weak	Yes	Yes
Lose weight	Equivocal	Equivocal	Yes[a]
Avoid alcoholic beverages	Weak	Mechanisms not understood; different alcoholic beverages have different effects	Not generally
Stop smoking	Weak	Yes	Yes[a]
Avoid excessive exercise	Weak	Yes	Yes
Sleep with head elevated	Equivocal	Equivocal	Yes
Sleep on the left side	Unequivocal	Yes	Yes

[a]Obesity and smoking seem to be risk factors for cancer of the distal esophagus.

Recommendations based on results of a review of studies involving lifestyle modifications

Table 1. Summary and strength of recommendations

	GRADE quality of evidence	GRADE strength of recommendation
Diagnosis of GERD		
For patients with classic GERD symptoms of heartburn and regurgitation who have no alarm symptoms, we recommend an 8-wk trial of empiric PPIs once daily before a meal.	Moderate	Strong
We recommend attempting to discontinue the PPIs in patients whose classic GERD symptoms respond to an 8-wk empiric trial of PPIs.	Low	Conditional
In patients with chest pain who have had adequate evaluation to exclude heart disease, objective testing for GERD (endoscopy and/or reflux monitoring) is recommended.	Low	Conditional
We do not recommend the use of a barium swallow solely as a diagnostic test for GERD.	Low	Conditional
We recommend endoscopy as the first test for evaluation of patients presenting with dysphagia or other alarm symptoms (weight loss and GI bleeding) and for patients with multiple risk factors for Barrett's esophagus.	Low	Strong
In patients for whom the diagnosis of GERD is suspected but not clear, and endoscopy shows no objective evidence of GERD, we recommend reflux monitoring be performed off therapy to establish the diagnosis.	Low	Strong
We suggest against performing reflux monitoring off therapy solely as a diagnostic test for GERD in patients known to have endoscopic evidence of LA grade C or D reflux esophagitis or in patients known to have long-segment Barrett's esophagus.	Low	Strong

GERD management		
We recommend weight loss in overweight and obese patients for improvement of GERD symptoms.	Moderate	Strong
We suggest avoiding meals within 2–3 hr of bedtime.	Low	Conditional
We suggest avoidance of tobacco products/smoking in patients with GERD symptoms.	Low	Conditional
We suggest avoidance of "trigger foods" for GERD symptom control.	Low	Conditional
We suggest elevating head of bed for nighttime GERD symptoms.	Low	Conditional
We recommend treatment with PPIs over treatment with H2RA for healing EE.	High	Strong
We recommend treatment with PPIs over H2RA for maintenance of healing for EE.	Moderate	Strong
We recommend PPI administration 30–60 min before a meal rather than at bedtime for GERD symptom control.	Moderate	Strong
For patients with GERD who do not have EE or Barrett's esophagus, and whose symptoms have resolved with PPI therapy, an attempt should be made to discontinue PPIs	Low	Conditional
For patients with GERD who require maintenance therapy with PPIs, the PPIs should be administered in the lowest dose that effectively controls GERD symptoms and maintains healing of reflux esophagitis.	Low	Conditional
We recommend against routine addition of medical therapies in PPI nonresponders.	Moderate	Conditional
We recommend maintenance PPI therapy indefinitely or antireflux surgery for patients with LA grade C or D esophagitis.	Moderate	Strong
We do not recommend baclofen in the absence of objective evidence of GERD.	Moderate	Strong
We recommend against treatment with a prokinetic agent of any kind for GERD therapy unless there is objective evidence of gastroparesis.	Low	Strong
We do not recommend sucralfate for GERD therapy except during pregnancy.	Low	Strong
We suggest on-demand/or intermittent PPI therapy for heartburn symptom control in patients with NERD.	Low	Conditional

Extraesophageal GERD symptoms		
We recommend evaluation for non-GERD causes in patients with possible extraesophageal manifestations before ascribing symptoms to GERD.	Moderate	Strong
We recommend that patients who have extraesophageal manifestations of GERD without typical GERD symptoms (e.g., heartburn and regurgitation) undergo reflux testing for evaluation before PPI therapy.	Moderate	Strong
For patients who have both extraesophageal and typical GERD symptoms, we suggest considering a trial of twice-daily PPI therapy for 8–12 wk before additional testing.	Low	Conditional
We suggest that upper endoscopy should not be used as the method to establish a diagnosis of GERD-related asthma, chronic cough, or LPR.	Low	Conditional
We suggest against a diagnosis of LPR based on laryngoscopy findings alone and recommend additional testing should be considered.	Low	Conditional
In patients treated for extraesophageal reflux disease, surgical or endoscopic antireflux procedures are only recommended in patients with objective evidence of reflux.	Low	Conditional
Refractory GERD		
We recommend optimization of PPI therapy as the first step in management of refractory GERD.	Moderate	Strong
We recommend esophageal pH monitoring (Bravo, catheter-based, or combined impedance-pH monitoring) performed OFF PPIs if the diagnosis of GERD has not been established by a previous pH monitoring study or an endoscopy showing long-segment Barrett's esophagus or severe reflux esophagitis (LA grade C or D).	Low	Conditional
We recommend esophageal impedance-pH monitoring performed ON PPIs for patients with an established diagnosis of GERD whose symptoms have not responded adequately to twice-daily PPI therapy.	Low	Conditional
For patients who have regurgitation as their primary PPI-refractory symptom and who have had abnormal gastroesophageal reflux documented by objective testing, we recommend consideration of antireflux surgery or TIF.	Low	Conditional

Surgical and endoscopic options for GERD		
We recommend antireflux surgery performed by an experienced surgeon as an option for long-term treatment of patients with objective evidence of GERD. Those who have severe reflux esophagitis (LA grade C or D), large hiatal hernias, and/or persistent, troublesome GERD symptoms who are likely to benefit most from surgery.	Moderate	Strong
We recommend consideration of MSA as an alternative to laparoscopic fundoplication for patients with regurgitation who fail medical management.	Moderate	Strong
We recommend consideration of RYGB as an option to treat GERD in obese patients who are candidates for this procedure and who are willing to accept its risks and requirements for lifestyle alterations.	Low	Conditional
Because data on the efficacy of radiofrequency energy (Stretta) as an antireflux procedure is inconsistent and highly variable, we cannot recommend its use as an alternative to medical or surgical antireflux therapies.	Low	Conditional
We suggest consideration of TIF for patients with troublesome regurgitation or heartburn who do not wish to undergo antireflux surgery and who do not have severe reflux esophagitis (LA grade C or D) or hiatal hernias >2 cm.	Low	Conditional

EE, erosive esophagitis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; H2RA, histamine-2-receptor antagonists; LA, Los Angeles; LPR, laryngopharyngeal reflux; MSA, magnetic sphincter augmentation; NERD, nonerosive reflux disease; PPI, proton pump inhibitor; TIF, transoral incisionless fundoplication; RYGB, Roux-en-Y gastric bypass.

Source: ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease
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(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 2. Key concept statements

Diagnosis of GERD
We do not recommend HRM solely as a diagnostic test for GERD.
GERD management
There is conceptual rationale for a trial of switching PPIs for patients who have not responded to one PPI. For patients who have not responded to one PPI, more than one switch to another PPI cannot be supported.
Use of the lowest effective dose is recommended and logical but must be individualized. One area of controversy relates to abrupt PPI discontinuation and potential rebound acid hypersecretion, resulting in increased reflux symptoms. Although this has been demonstrated to occur in healthy controls, strong evidence for an increase in symptoms after abrupt PPI withdrawal is lacking.
Extraesophageal GERD
Although GERD may be a contributor to extraesophageal symptoms in some patients, careful evaluation for other causes should be considered for patients with laryngeal symptoms, chronic cough, and asthma.
Diagnosis, evaluation, and management of potential extraesophageal symptoms of GERD is limited by lack of a gold-standard test, variable symptoms, and other disorders which may cause similar symptoms
Endoscopy is not sufficient to confirm or refute the presence of extraesophageal GERD.
Because of difficulty in distinguishing between patient with laryngeal symptoms and normal controls, salivary pepsin testing is not recommended for evaluation of patients with extraesophageal reflux symptoms
For patients whose extraesophageal symptoms have not responded to a trial of twice-daily PPIs, we recommend upper endoscopy, ideally off PPIs for 2–4 wk. If endoscopy is normal, consider reflux monitoring. If EGD shows EE, that does not confirm that the extraesophageal symptoms are from GERD. Patients still may need pH-impedance testing
For patients with extraesophageal symptoms, we do not routinely recommend oropharyngeal or pharyngeal pH monitoring.

Refractory GERD
It is important to stop PPI therapy in patients whose off-therapy reflux testing is negative, unless another indication for continuing PPIs is present. In 1 study, 42% of patients reported continuing PPI treatment after a negative evaluation for refractory GERD, which included negative endoscopy and pH-impedance monitoring [2].
Esophageal manometry should be considered as part of the evaluation for patients with refractory GERD in patients with a normal endoscopy and pH monitoring study and for patients being considered for surgical or endoscopic treatment.
If not already performed off PPIs, we recommend diagnostic upper endoscopy with esophageal biopsies after discontinuing PPI therapy, ideally for 2 to 4 wk
For patients with PPI-refractory symptoms who have a normal pH monitoring test OFF PPIs or a normal impedance-pH monitoring test ON PPIs (including a negative SI and SAP), we recommend discontinuation of PPIs unless there is an indication for PPI therapy other than the refractory symptoms.
Surgical and endoscopic therapy
We recommend HRM before antireflux surgery or endoscopic therapy to rule out achalasia and absent contractility. For patients with ineffective esophageal motility, HRM should include provocative testing to identify contractile reserve (e.g., multiple rapid swallows).
We recommend a careful evaluation and caution before proceeding with invasive therapy for patients with PPI-refractory GERD symptoms other than regurgitation.
Before performing invasive therapy for GERD, a careful evaluation is required to ensure that GERD is present and as best as possible determine is the cause of the symptoms to be addressed by the therapy, to exclude achalasia (which can be associated with symptoms such as heartburn and regurgitation that can be confused with GERD), and to exclude conditions that might be contraindications to invasive treatment such as absent contractility.

Long-term PPI issues
Regarding the safety of long-term PPI usage for GERD, we suggest that patients should be advised as follows: "PPIs are the most effective medical treatment for GERD. Some medical studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. Those studies have flaws, are not considered definitive, and do not establish a cause-and-effect relationship between PPIs and the adverse conditions. High-quality studies have found that PPIs do not significantly increase the risk of any of these conditions except intestinal infections. Nevertheless, we cannot exclude the possibility that PPIs might confer a small increase in the risk of developing these adverse conditions. For the treatment of GERD, gastroenterologists generally agree that the well-established benefits of PPIs far outweigh their theoretical risks."
Switching PPIs can be considered for patients who experience minor PPI side effects including headache, abdominal pain, nausea, vomiting, diarrhea, constipation, and flatulence.
For patients with GERD on PPIs who have no other risk factors for bone disease, we do not recommend that they raise their intake of calcium or vitamin D or that they have routine monitoring of bone mineral density.
For patients with GERD on PPIs who have no other risk factors for vitamin B12 deficiency, we do not recommend that they raise their intake of vitamin B12 or that they have routine monitoring of serum B12 levels.
For patients with GERD on PPIs who have no other risk factors for kidney disease, we do not recommend that they have routine monitoring of serum creatinine levels.
For patients with GERD on clopidogrel who have LA grade C or D esophagitis or whose GERD symptoms are not adequately controlled with alternative medical therapies, the highest quality data available suggest that the established benefits of PPI treatment outweigh their proposed but highly questionable cardiovascular risks.
PPIs can be used to treat GERD in patients with renal insufficiency with close monitoring of renal function or consultation with a nephrologist.
EE, erosive esophagitis; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; LA, Los Angeles; PPI, proton pump inhibitor; SAP, symptom association probability; SI, symptom index.

Source: ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease
Official journal of the American College of Gastroenterology | ACG117(1):27-56, January 2022.

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	• H2RAs are for more mild, intermittent symptoms.
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

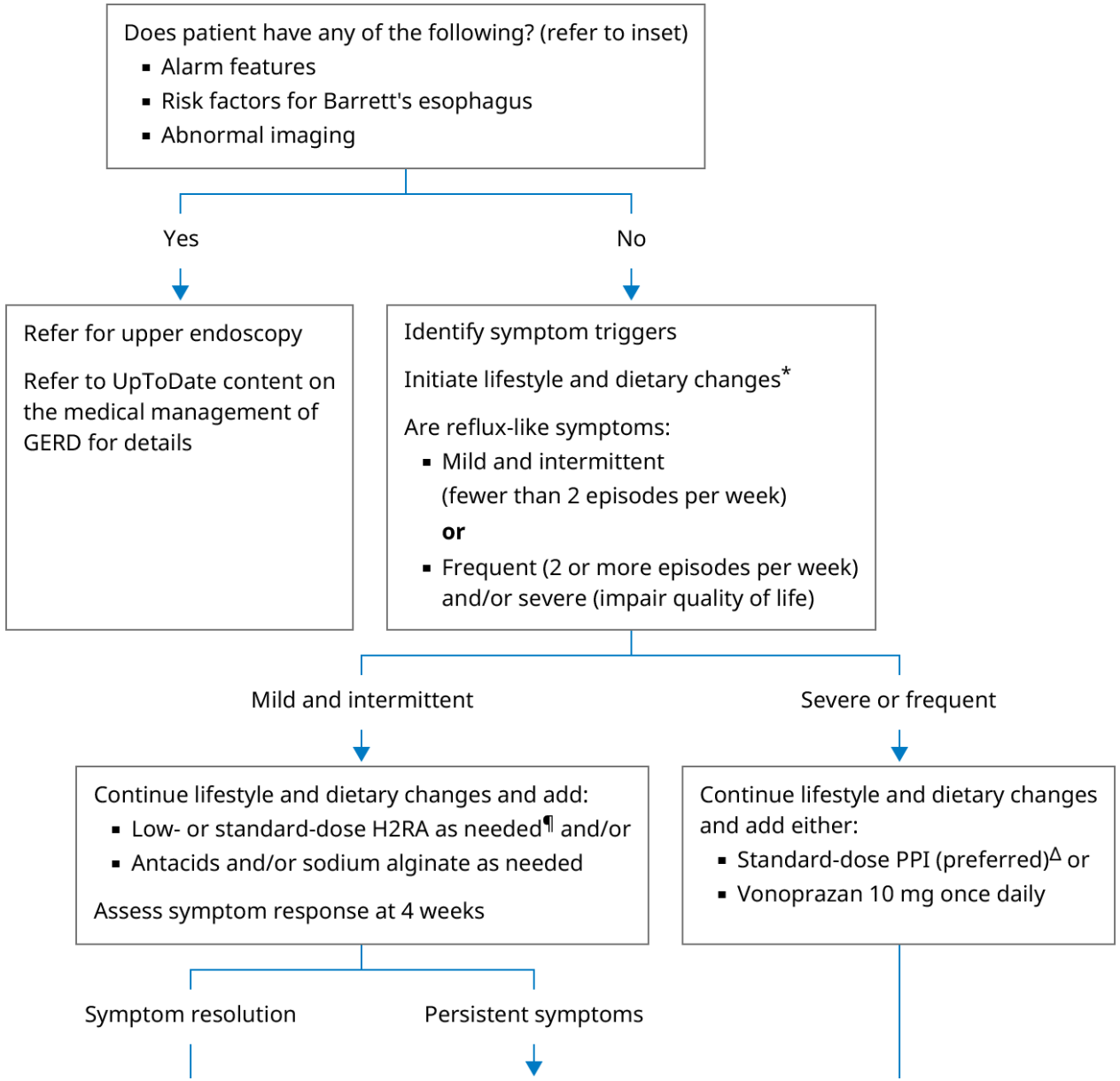
Potassium-Competitive Acid Blocker		
Vonoprazan	10 mg daily	Relief of heartburn associated with nonerosive GERD

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	

Potassium-Competitive Acid Blocker		
Vonoprazan	20 mg daily	Indicated for healing of all grades of erosive esophagitis and heartburn associated with erosive esophagitis in adults. Also indicated for the maintenance of healed erosive esophagitis (10 mg once daily).

Initial empiric management of adults with reflux-like symptoms (UpToDate)



Alarm symptoms suggestive of gastrointestinal malignancy

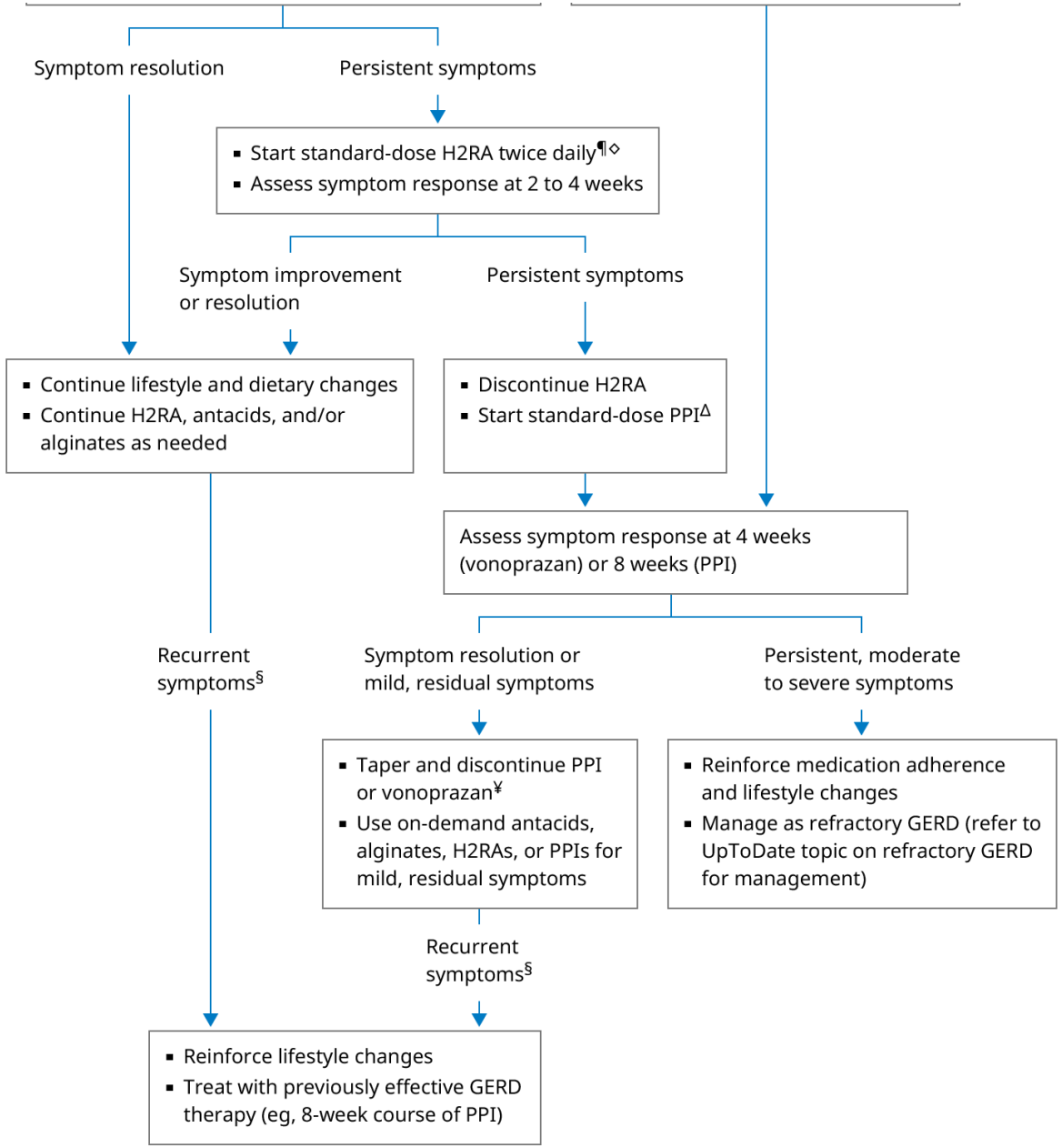
- New-onset dyspepsia in patient ≥60 years old
- Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
- Iron deficiency anemia
- Anorexia
- Unexplained weight loss
- Dysphagia or odynophagia
- Persistent vomiting
- Gastrointestinal cancer in a first-degree relative

Risk factors for Barrett's esophagus‡

- Chronic GERD (at least 5 years of persistent symptoms) plus 3 of the following additional risk factors:
  - Age >50 years
  - Male sex
  - Non-Hispanic White individual
  - Obesity
  - Tobacco use (past or current)
  - First-degree relative with Barrett's esophagus or esophageal adenocarcinoma

Abnormal imaging

- Luminal abnormality on imaging of upper gastrointestinal tract


Symptom resolution
Persistent symptoms
▪ Start standard-dose H2RA twice daily¶◇
▪ Assess symptom response at 2 to 4 weeks
Symptom improvement or resolution
Persistent symptoms
▪ Continue lifestyle and dietary changes
▪ Continue H2RA, antacids, and/or alginates as needed
▪ Discontinue H2RA
▪ Start standard-dose PPIΔ
Assess symptom response at 4 weeks (vonoprazan) or 8 weeks (PPI)
Recurrent symptoms§
Symptom resolution or mild, residual symptoms
Persistent, moderate to severe symptoms
▪ Taper and discontinue PPI or vonoprazan¥
▪ Use on-demand antacids, alginates, H2RAs, or PPIs for mild, residual symptoms
▪ Reinforce medication adherence and lifestyle changes
▪ Manage as refractory GERD (refer to UpToDate topic on refractory GERD for management)
Recurrent symptoms§
▪ Reinforce lifestyle changes
▪ Treat with previously effective GERD therapy (eg, 8-week course of PPI)

This algorithm shows the initial empiric management of adults with reflux-like symptoms. Most patients with typical reflux-like symptoms of heartburn or regurgitation are candidates for empiric treatment.
* Identify symptom triggers (eg, nocturnal symptoms, large meals, alcohol, soda intake, tobacco use, or specific foods), and individualize lifestyle changes to address them.

¶ Low-dose H2RA options include twice-daily cimetidine 200 mg, famotidine 10 mg, and nizatidine 75 mg. Standard-dose H2RA options include twice-daily cimetidine 400 mg, famotidine 20 mg, and nizatidine 150 mg.

Δ Standard-dose PPI options include once-daily dexlansoprazole 30 mg, esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, or rabeprazole 20 mg.

◊ If patient had no response to intermittent H2RA therapy, start PPI rather than twice-daily H2RA. Refer to UpToDate content for details.

§ Approximately two-thirds of adults with GERD will have recurrent symptoms. Patients whose symptoms recur <3 months after discontinuing PPI or vonoprazan may require maintenance acid suppression. Patients without recurrent symptoms should continue lifestyle and dietary modifications.

¥ Tapering is not required for short (eg, <6 months) duration of treatment. Refer to UpToDate content for details regarding tapering and discontinuing PPI or vonoprazan.

‡ Professional guidelines provide different criteria for screening for Barrett's esophagus and are based predominantly on expert consensus.

Antisecretory medications for gastroesophageal reflux disease in nonpregnant adults (UpToDate)

Medication	Low dose	Standard dose	High dose*
Histamine 2 receptor antagonists¶			
Cimetidine[Δ]	200 mg twice daily[◇]	400 mg twice daily	Not recommended
Famotidine	10 mg twice daily[◇]	20 mg twice daily[◇]	40 mg twice daily
Nizatidine	75 mg twice daily[§]	150 mg twice daily	300 mg twice daily
Proton pump inhibitors			
Dexlansoprazole	Not available	30 mg once daily	60 mg once or twice daily
Esomeprazole	20 mg once daily[◇]	40 mg once daily	40 mg twice daily
Lansoprazole	15 mg once daily[◇]	30 mg once daily	30 mg twice daily
Omeprazole	Not recommended[¥]	20 mg once daily[◇]	40 mg twice daily
Pantoprazole	20 mg once daily	40 mg once daily	40 mg twice daily
Rabeprazole	10 mg once daily[‡]	20 mg once daily	20 mg twice daily
Potassium-competitive acid blockers			
Vonoprazan[†]	10 mg once daily	20 mg once daily	20 mg twice daily

Antisecretory medications for gastroesophageal reflux disease in nonpregnant adults (UpToDate)

Dosing in this table is for oral administration in adults with normal kidney and liver function. For additional information, including dose adjustments, refer to drug monographs.

Standard-dose PPI regimens are typically used when PPI therapy is initiated. Low-dose PPI regimens may be useful for tapering off PPI therapy. High-dose PPI regimens are commonly used in instances of inadequate treatment response to standard-dose PPI regimens, although they may not have regulatory approval. Doses for different PPIs within each category do not necessarily provide equivalent intragastric 24-hour acid suppression.

High-dose H2RA regimens are uncommonly used as they are unlikely to confer greater symptom control than standard-dose regimens.

H2RA: histamine 2 receptor antagonist; PPI: proton pump inhibitor.

* Twice-daily doses of PPIs and vonoprazan are used clinically but may not have regulatory approval.

¶ H2RAs require dose adjustment for kidney impairment.

Δ Significant drug interactions can occur. When initiating or altering drug therapy, use of a drug interactions program is advised.

◊ Available without a prescription (over the counter) in the United States and elsewhere; consult local product availability.

§ Not available in the United States. Consult local product availability.

¥ In some countries outside the United States, omeprazole 10 mg once daily is approved for maintenance of symptom relief after initial standard-dose therapy.

‡ In some countries, dose strength is limited to certain dose forms (eg, sprinkle capsule), which may be costlier. Consult local product availability.

† Vonoprazan should not be used in persons who are pregnant or breastfeeding.

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 • Chronic kidney disease	• 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, ≥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
Potassium-Competitive Acid Blocker			
Vonoprazan	Similar adverse, short-term, and long-term effects as PPIs	Similar monitoring parameters as PPIs	See comments for PPIs

For you own knowledge

Table 5. Major putative adverse effects of chronic PPI therapy

Putative adverse effect	Meta-analysis reference numbers	HR[a] or OR[b] (95% CI) found in recent RCT (94)	Major proposed mechanisms
Cardiovascular events (All) MI Stroke Cardiovascular death	(237–240)	1.04[a] (0.93–1.15) 0.94[a] (0.79–1.12) 1.16[a] (0.94–1.44) 1.03[a] (0.89–1.20)	PPIs block metabolism of ADMA, which accumulates and inhibits NO synthase, thus blocking endothelial production of NO needed for vascular homeostasis
Cardiovascular events in patients on clopidogrel[c]	(241–260)	NA	PPIs are metabolized by the same enzyme needed to activate clopidogrel (CYP2C19), so concomitant use of these drugs might decrease the antiplatelet effect of clopidogrel
Kidney disease (All) AIN Chronic kidney disease	(261–265)	NA NA 1.17[b] (0.94–1.45)	AIN develops as an idiosyncratic drug reaction and progresses to chronic kidney disease
Enteric infection (other than *Clostridium. difficile*)	(266,267)	1.33[b] (1.01–1.75)	Reduced gastric acid enables ingested enteric pathogens to survive passage through the stomach
C. difficile	(268–276)	2.26[b] (0.70–7.34)	Reduced gastric acid enables survival of ingested *C. difficile* vegetative forms and prevents conversion of salivary nitrite to ROS that suppress *C. difficile* spores; PPIs may enhance *C. difficile* toxin expression and cause microbiome alterations that promote *C. difficile* colitis
SIBO	(277,278)	NA	Reduced gastric acid enables increased bacterial colonization of the UGI tract
Spontaneous bacterial peritonitis in patients with cirrhosis	(279–283)	NA	Increased bacterial colonization of the UGI tract and PPI-induced increases in UGI tract permeability predispose to bacterial translocation; PPIs also might interfere with inflammatory cell functions that ordinarily would prevent infection
Pneumonia	(284–289)	1.02[b] (0.87–1.19)	Reduced gastric acid enables UGI tract colonization with pulmonary pathogens that can be aspirated; PPIs also might interfere with inflammatory cell functions that ordinarily would prevent infection
Dementia	(290–293)	1.20[b] (0.81–1.78)	PPIs block vacuolar H^+-ATPase needed to acidify microglial lysosomes, thereby preventing their degradation of cerebral amyloid-β peptide; PPI-induced B12 deficiency also might contribute to dementia

Bone fracture	(294–302)	0.96[b] (0.79–1.17)	Reduced gastric acid causes calcium malabsorption leading to decreased bone mineral density; PPIs might reduce bone resorption by blocking vacuolar H^+-ATPase in osteoclasts; PPIs cause hypergastrinemia that might cause parathyroid hyperplasia
Gastric atrophy	(303–305)	0.73[b] (0.40–1.32)	PPIs promote corpus-predominant *H. pylori* gastritis that results in gastric atrophy with loss of parietal cells
Gastric cancer	(306–308)	NA	PPIs promote gastric atrophy and inflammation in *H. pylori*–infected patients, resulting in intestinal metaplasia predisposed to malignancy; reduced gastric acid enables overgrowth of bacteria that convert dietary nitrates to potentially carcinogenic N-nitroso compounds; PPI-induced hypergastrinemia causes gastric epithelial cell proliferation that promotes carcinogenesis
Vitamin B12 deficiency	(309)	NA	Reduced gastric acid results in malabsorption of protein-bound cobalamin; gastric atrophy results in decreased intrinsic factor production
Hypomagnesemia	(310–312)	NA	PPI effects in elevating intestinal pH may interfere with magnesium absorption, perhaps because the affinity of the enterocyte magnesium transporter TRPM6/7 for magnesium decreases in a higher pH environment
All-cause mortality	(313)	1.03[a] (0.92–1.15)	Potentially all of above

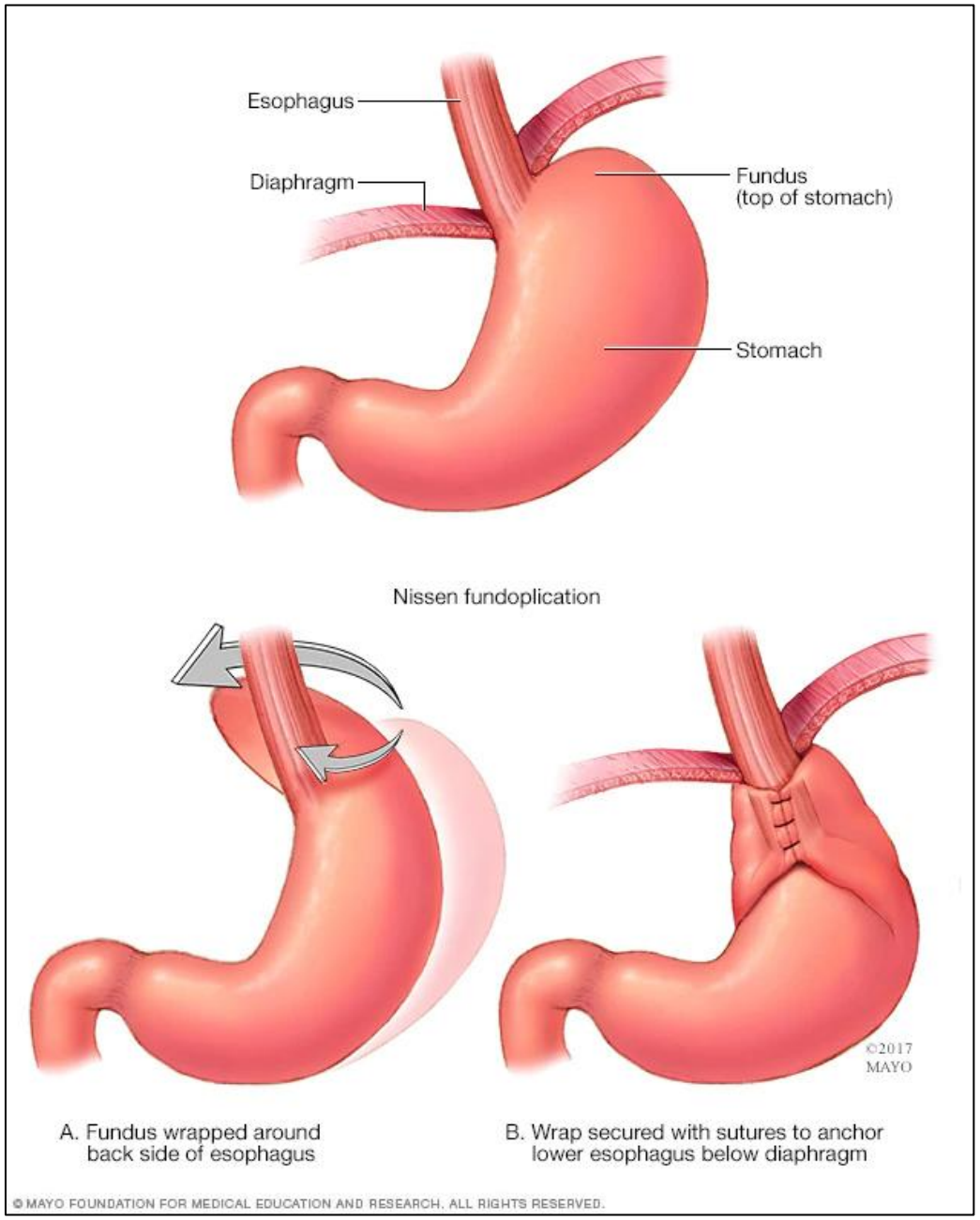
[a]Hazard ratio.
[b]Odds ratio
[c]The US Food and Drug Administration recommends avoiding the concomitant use of clopidogrel and omeprazole.
ADMA, asymmetric dimethylarginine; AIN, acute interstitial nephritis; ATP, adenosine triphosphate; CI, confidence interval; HR, hazard ratio; MI, mucosal integrity; NA, not available; NO, nitric oxide; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomized controlled trial (94); ROS, reactive oxygen species; SIBO, small intestinal bacterial overgrowth; TRPM6/7, transient receptor potential melastatin 6 and 7.

✓ 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

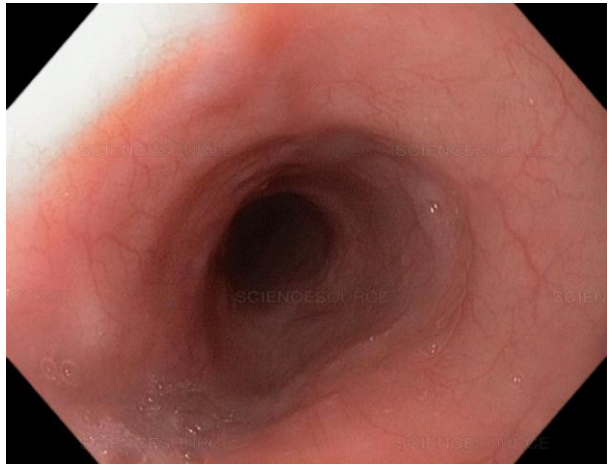
- When symptoms are controlled on PPI therapy, medical therapy and fundoplication are equally effective.

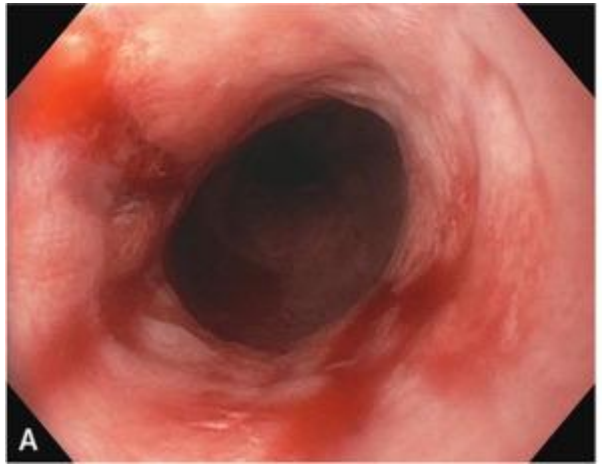
- Although fundoplication could provide better symptom control and quality of life in the short term, new postoperative symptoms and surgical failure can also occur.

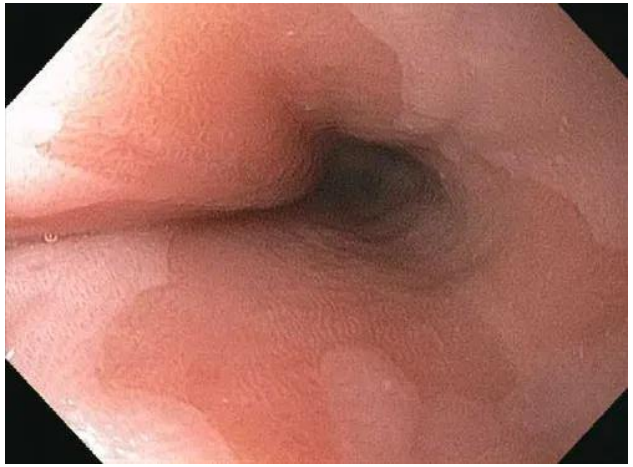


Complications

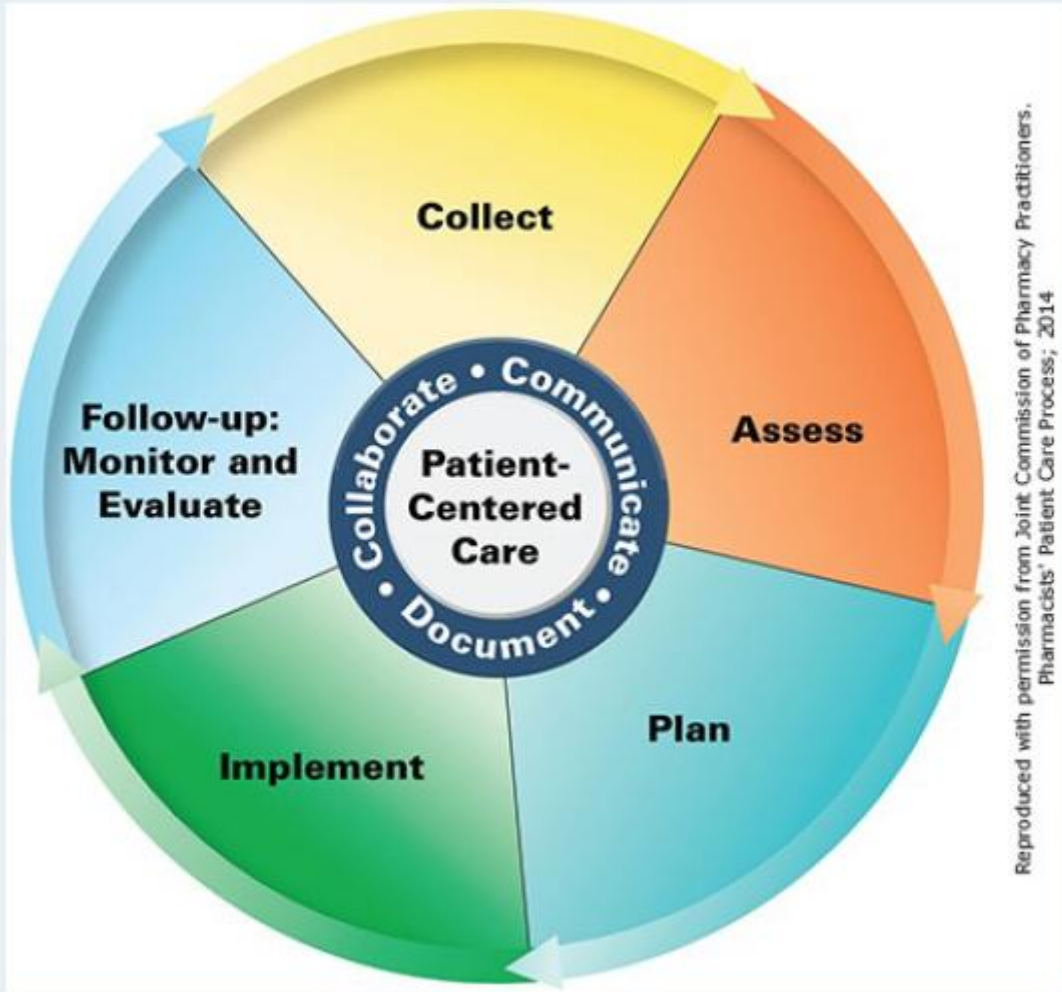
- ✓ Esophageal erosion and ulceration (esophagitis) can rarely lead to overt bleeding and IDA.
- ✓ Strictures can form when esophagitis heals, leading to dysphagia. Endoscopic dilation and maintenance PPI therapy typically resolve dysphagia from strictures.
- ✓ Barrett esophagus (BE) is a reflux-triggered 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).







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, serum creatinine)

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 53-1)
- Review medication profile for medications that may be contributing to symptoms (see Table 53-1) 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 53-4)
- Determine appropriate therapy (may include both nonpharmacologic and pharmacologic) based on patient's presentation (see Table 53-2)
- For pharmacologic therapy, include medication name, dose, route, frequency, and duration of therapy recommendation (see Table 53-3)
- 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 53-5)
- Identify patient education that may be needed (eg, purpose of medication, mechanism of action, individualized lifestyle modifications, adverse effects, administration clinical pearls, adherence, and potential need for long-term maintenance therapy
- For refractory symptoms, seek potential causes such as medication adherence, timing of medication, drug interactions, and nonacid-related disorders
- Screen for symptoms that would require further diagnostic evaluation from clinician (eg, alarm symptoms, extraesophageal 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) (see Table 53-4)
- Initiate appropriate nonpharmacologic and pharmacologic therapy based on patient presentation (see Tables 53-2 and 53-3)
- 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) mechanism of action; (d) what potential adverse effects (including long-term adverse effects) or drug interactions may occur
- Provide education to increase awareness about the brain-gut axis relation to patients with reflux symptoms and the benefits of relaxation strategies
- 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 PPI therapy. Attempt to de-prescribe PPIs if possible or use lowest effective dose.
- Monitor patient for goals of therapy.
- 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 to the patient of medication adherence to treatment plan as indicated.
- Review and document the ongoing indication for PPI use.

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