CME CREDIT **EDUCATIONAL OBJECTIVE:** Readers will diagnose and treat gastroesophageal reflux disease confidently

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GERD: Diagnosing and treating the burn

ABSTRACT

Gastroesophageal reflux disease (GERD) is chronic, very common, and frequently encountered in internal medicine and subspecialty clinics. It is often diagnosed on clinical grounds, but specialized testing such as endoscopy and pH monitoring may be necessary in certain patients. Although proton pump inhibitors (PPIs) are the mainstay of treatment, clinicians should be aware of their short-term and long-term side effects.

KEY POINTS

GERD symptoms may be typical (eg, heartburn, regurgitation) or atypical (eg, cough, chest pain, hoarseness).

In patients with typical symptoms, a 6- to 8-week trial of a PPI is a reasonable and cost-effective approach to diagnosing GERD.

Endoscopy is indicated for patients who have alarm symptoms such as dysphagia, weight loss, and bleeding; it is unnecessary in patients who have typical GERD symptoms.

Ambulatory pH monitoring should be used in patients whose symptoms do not respond to a PPI and those in whom antireflux surgery is being considered.

Weight loss and head-of-bed elevation are the only lifestyle interventions that have been proven effective for GERD.

While risks of PPI use are rare, they should be discussed with patients on long-term therapy.

Symptoms that do not respond to a PPI are less likely to improve with antireflux surgery.

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Gastroesophageal reflux disease (GERD) is a chronic and common medical problem, with up to 40% of the population experiencing its symptoms at least once per month.[1] The condition develops when the reflux of stomach contents causes troublesome symptoms or complications.[2]

GERD symptoms can range from heartburn and regurgitation to cough and hoarseness. While many patients' symptoms respond to medical treatment, the diagnosis and treatment in those whose symptoms do not respond to a proton pump inhibitor (PPI) may be challenging.

This article reviews the diagnosis and treatment options for GERD.

SYMPTOMS: TYPICAL, ATYPICAL, AND ALARM

Symptoms of GERD (**Table 1**) can be classified as typical (heartburn and regurgitation) or atypical (cough, asthma, hoarseness, chronic laryngitis, throat-clearing, chest pain, dyspepsia, and nausea). Atypical symptoms are more likely to be due to GERD if patients also have typical symptoms and if the symptoms respond to a trial of a PPI.[3]

Alarm symptoms. Keep in mind that extraesophageal presentations may be multifactorial, and it may be difficult to establish that reflux, even if present, is actually the cause. While chest pain may be due to GERD, it is important to rule out cardiac chest pain before considering GERD as a cause. Similarly, dysphagia along with typical or atypical symptoms warrants investigation for potential complications such as underlying motility disorder, esophageal stricture, esophageal ring, or malignancy.[4] Other alarm symptoms include odynophagia, bleeding, weight loss, and anemia.

TABLE 1

Classification of gastroesophageal reflux disease symptoms

Typical symptoms	Heartburn and regurgitation
Atypical symptoms	Chronic cough, asthma, hoarseness, chronic laryngitis, throat-clearing, chest pain, dyspepsia, nausea
Alarm symptoms	Dysphagia, odynophagia, bleeding, weight loss, anemia, chest pain

DIAGNOSING GERD: RESPONSE TO A PPI IS DIAGNOSTIC

Patients with typical symptoms that respond to PPI therapy need no further evaluation for a diagnosis of GERD to be made.[5] On the other hand, further testing should be undertaken in patients with typical symptoms that do not respond to PPI therapy, in patients presenting with atypical symptoms, and in patients in whom antireflux surgery is being considered. **Figure 1** shows our proposed algorithm.

While chest pain may be a primary symptom of GERD, cardiac chest pain must be ruled out

Try a PPI for 6–8 weeks

Relief of heartburn and regurgitation after a 6- to 8-week course of a PPI strongly suggests GERD.[6] However, a negative trial of a PPI does not rule out GERD, as this approach has been found to have a sensitivity of 78% and specificity of 54%.[6]

Despite this limitation, a trial of PPI therapy should be offered to patients presenting with typical symptoms and no alarm features. This approach has been found to be more cost-effective than proceeding directly to diagnostic testing.[7]

Endoscopy

Endoscopic findings in GERD can include erosive esophagitis, peptic stricture, and Barrett esophagus. Esophageal erosions are a highly specific sign of GERD; the Los Angeles classification system, a standardized scale for grading the severity of erosive esophagitis (from A to D, with D the most severe) provides an objective way to assess severity.[8] However, most patients with heartburn and regurgitation do not have erosive disease, thus limiting the sensitivity of upper endoscopy as an initial diagnostic test in patients with suspected GERD.[9]

We recommend endoscopy for patients who present with alarm symptoms, patients with noncardiac chest pain, PPI nonresponders, and patients with chronic GERD symptoms and multiple risk factors for Barrett esophagus besides GERD, such as older age, male sex, white race, overweight, and smoking.[10]

Ambulatory pH and impedance monitoring

Ambulatory pH monitoring is the gold standard test for pathologic acid exposure in the esophagus. pH testing is indicated in PPI nonresponders, patients presenting with atypical symptoms, and before antireflux surgery.

In general, pH testing should be performed after the patient has been off PPI therapy for at least 7 days, as the test is highly unlikely to be abnormal while a patient is on a PPI.[11] It is done either with a transnasal catheter for 24 hours, or with a wireless capsule (Bravo pH System, Given Imaging Ltd, Duluth, GA), which collects 48 to 96 hours of data. Studies of the wireless system have shown that its sensitivity increases 12% to 25% when it is performed for 48 hours compared with 24 hours.[12,13]

The pH test can be combined with impedance testing to evaluate for nonacid reflux.[14] However, the clinical significance of nonacid reflux remains controversial, and for this reason the Esophageal Diagnostic Advisory Panel recommends that the decision to perform antireflux surgery should not be based on abnormal impedance testing.[15]

During pH and impedance testing, special software can calculate how closely the patient's symptoms correlate with esophageal acid exposure. The symptom index (SI) and symptom association probability (SAP) are the symptom measurements most commonly used in practice. The SI measures the overall strength of the relationship, and an SI greater than 50% is considered positive.[16] The SAP determines whether this relationship could have occurred by chance, and an SAP greater than 95% is statistically significant.[17] In patients with normal levels of esophageal acid exposure, an elevated SI or SAP may indicate a component of esophageal hypersensitivity in symptom generation.

At our institution, we generally perform pH-only transnasal or wireless testing off PPI

Algorithm for diagnosing and treating gastroesophageal reflux disease (GERD)

Step 1: Does the patient have alarm symptoms? (see **Table 1**)

Yes – Perform esophagogastroduodenoscopy (EGD); if EGD is unremarkable, proceed to step 2

No – Proceed to step 2

Step 2: Did an 8-week course of a proton pump inhibitor (PPI) relieve the symptoms?

Yes – The patient has PPI-responsive GERD; taper PPI to lowest effective dose

No – Consider referral to gastroenterologist; may proceed to EGD and pH testing (off PPI for 7 days), then proceed to step 3

Options for pH testing:
- 24-hour pH catheter with esophageal manometry
- 48-hour wireless pH capsule placed during EGD

Step 3: Does the patient have objective evidence of GERD?
(erosive esophagitis or Barrett esophagus on EGD; abnormal acid exposure on pH testing)

Yes – The patient has GERD

Discuss management strategies

May consider antireflux surgery; however, symptoms that do not respond to PPIs are less likely to respond to surgery

Proceed to step 4 if symptoms persist

No – The patient does not have GERD

If typical symptoms of heartburn or regurgitation are present but pH testing is negative, the patient may have functional heartburn or functional dyspepsia; consider referral to gastroenterologist specializing in functional disorders

If atypical symptoms are present (eg, cough, hoarseness, asthma) but pH testing is negative, GERD is likely not the cause; consider referral as necessary (pulmonologist, otolaryngologist, allergist)

Step 4: Does the patient have nonacid reflux on combined pH-impedance testing?

Yes – The patient has GERD and nonacid reflux despite PPI therapy; can consider antireflux surgery, but symptoms that do not respond to PPI therapy are less likely to respond to surgery

No – The patient has GERD and possible functional overlap with acid-sensitive esophagus; continue GERD management strategies and consider referral to gastroenterologist specializing in functional disorders

FIGURE 1.

A negative trial of a PPI does not rule out GERD

therapy to establish that the patient has pathologic acid exposure in the distal esophagus. Combined pH-impedance testing is typically reserved for patients with atypical symptoms unresponsive to PPI therapy and abnormal results on previous pH testing, which allows for correlation of nonacid reflux and symptoms.

Other tests

Esophageal manometry and barium esophagography have limited value in the primary diagnosis of GERD. However, they should be considered to rule out achalasia and other esophageal motility disorders in patients whose symptoms do not respond to PPIs. For this

TABLE 2

Our treatment recommendations for gastroesophageal reflux disease (GERD)

	When to use
Lifestyle interventions	All patients with GERD
Antacids	As needed in patients with infrequent symptoms
Proton pump inhibitors	Patients with frequent symptoms
Histamine-2 receptor antagonists	Patients who cannot tolerate proton pump inhibitors
Sodium alginate	Patients with continued typical symptoms despite proton pump inhibitor therapy
Baclofen	May be used in patients with continued typical symptoms despite proton pump inhibitor therapy
Antireflux surgery	May be considered in patients with symptoms responsive to proton pump inhibitors and objective evidence of GERD

Ambulatory pH monitoring is the gold-standard test

reason, esophageal manometry should be performed before considering antireflux surgery.

MANAGING GERD

Table 2 summarizes the various treatments for GERD.

Lifestyle modifications

Lifestyle modifications are the first-line therapy for GERD. Modifications that have been studied include weight loss, head-of-bed elevation, and avoidance of tobacco, alcohol, and late-night meals. Another modification that has been suggested is avoiding foods that can aggravate reflux symptoms—eg, caffeine, coffee, chocolate, spicy foods, highly acidic foods (oranges, tomatoes), and fatty foods. Of these, only weight loss and head-of-bed elevation have been proven effective.[18]

Three randomized controlled trials demonstrated that GERD symptoms and esophageal pH values improved with head-of-bed elevation using blocks or incline foam wedges.[19–21] Several cohort studies demonstrated reduction in GERD symptoms with weight loss.[22,23] Recently, a prospective cohort study also found that smoking cessation significantly improved GERD symptoms in patients with normal body mass index and severe symptoms.[24]

Antacids

Several antacids (eg, sodium bicarbonate, calcium carbonate, magnesium hydroxide, aluminum hydroxide) are available over the counter.

Antacids were thought to control heartburn symptoms by increasing the pH of gastric contents that might subsequently reflux into the esophagus. However, well-controlled studies have shown that they relieve heartburn by neutralizing acid in the esophagus, with no significant effect on gastric pH.[25,26]

Antacids provide rapid but short-lived relief from an existing episode of heartburn. Because they do not significantly raise the gastric pH, they do not prevent subsequent reflux episodes from repeatedly exposing the esophagus to gastric acid and causing heartburn. Additionally, antacids have not been shown to contribute to healing of erosive esophagitis.[27] Hence, they may not be optimal for treating frequent reflux heartburn.

Sodium alginate

Gastric acid pockets are unbuffered pools of acid that float on top of ingested food.[28] They develop as a result of poor mixing of newly secreted acid and food in the proximal stomach, which remains relatively quiescent after a meal compared with the distal stomach.[29] In GERD, proximal extension of the acid pocket above the diaphragm increases the risk of acid reflux.[30] The acid pocket is therefore an important source of postprandial acid in GERD and, as such, represents a unique therapeutic target.

Emerging evidence suggests that alginates may act directly on the acid pocket. Alginates are natural polysaccharide polymers that, on contact with gastric acid, precipitate within minutes into a low-density viscous gel of near-neutral pH. The change in pH triggers the sodium bicarbonate in the formulation to release carbon dioxide that becomes trapped in the alginate gel, causing it to float to the top of the gastric contents like a raft.[31]

A randomized controlled trial demonstrated that sodium alginate was as effective as omeprazole in relieving symptoms in patients with nonerosive reflux disease.[32] Alginate has also been shown to provide more postprandial reflux relief than antacids.[33]

Histamine-2 receptor antagonists

Histamine-2 receptor antagonists act more swiftly and increase postprandial gastric pH more rapidly than PPIs, thus making them a good option for prophylaxis against postprandial GERD.[34] Taking these drugs at bedtime may help in patients with objective nighttime reflux despite optimal PPI use. However, tachyphylaxis may occur as early as 1 week after starting combination therapy.[35]

Proton pump inhibitors

There are currently seven available PPIs, including four that can be obtained over the counter (omeprazole, lansoprazole, esomeprazole, and omeprazole-sodium bicarbonate) and three available only by prescription (rabeprazole, pantoprazole, and dexlansoprazole). Studies have shown than a standard 6- to 8-week course of a PPI provides complete symptom relief in 70% to 80% of patients with erosive reflux disease and in 60% of patients with nonerosive reflux disease.[36,37] Clinically, PPIs all appear to be similar in their symptom relief.[38]

Most PPIs should be taken 30 to 60 minutes before meals. Exceptions are omeprazole-sodium bicarbonate and dexlansoprazole, which can be taken without regard to meals. At our institution, we usually start PPIs in a once-daily standard dose for 6 to 8 weeks and consider increasing to twice-daily dosing if symptoms do not respond completely. Patients with mild intermittent GERD symptoms may benefit from "on-demand" use of PPIs. This approach is best suited for patients with nonerosive reflux disease without evidence of Barrett esophagus on endoscopy.

Safety and adverse effects of PPIs

PPIs are generally safe but can cause adverse effects (**Table 3**).

Osteoporosis. In 2010, the US Food and Drug Administration issued warnings regarding the potential for wrist, hip, and spine fractures in PPI users.[26] Most recent evidence suggests that PPIs may be associated with a small increase in risk of hip fractures in patients already at high risk.[39,40] However, the 2013 American College of Gastroenterology (ACG) guidelines say that patients with known osteoporosis can remain on PPI therapy, and concern for hip fractures and osteoporosis should not affect the decision to use PPIs long-term except in patients with other risk factors for hip fracture.[41]

TABLE 3

Potential adverse effects of proton pump inhibitors (PPIs)

Osteoporosis
Risk is low and should only affect decision to use a PPI in patients with multiple risk factors for hip fracture

Community-acquired pneumonia
Slight increased risk with short-term PPI use, no increased risk with long-term use

***Clostridium difficile* infection**
Low risk; judicious use of PPIs is recommended in patients at high risk of *C difficile* infection

Hypomagnesemia
Low risk; consider monitoring levels in patients on chronic PPI therapy

Interaction with clopidogrel
No increased risk of cardiovascular events, and PPI use does not need to be altered in clopidogrel users

Of the lifestyle interventions for GERD, only weight loss and head-of-bed elevation have been proven effective

Community-acquired pneumonia. An increased risk of community-acquired pneumonia cannot be clearly documented in association with PPI therapy. Multiple studies, including randomized controlled trials, investigated this potential correlation. However, evidence suggests that short-term but not long-term PPI use may be associated with an overall increased risk of community-acquired pneumonia.[42,43] Current guidelines suggest that in patients who need a PPI, the drug should not be withheld on the basis of a potential risk of community-acquired pneumonia.[41]

***Clostridium difficile* infection.** In theory, PPIs may increase the risk of C *difficile* infection by increasing the ability of the spore to convert to the vegetative form and to survive intraluminally. In fact, studies and meta-analyses have suggested that PPIs do increase the risk of development and recurrence of C *dif-*

ficile infection.[44,45] Therefore, PPIs should be used with care in patients who are at risk.[41]

Interaction with clopidogrel. The antiplatelet activity of clopidogrel requires activation by CYP2C19, the same pathway required for metabolism of some PPIs. Concern was raised about decreased antiplatelet activity of clopidogrel in the presence of PPIs. This was extensively studied, and there now appears to be no increased risk of adverse cardiovascular events in patients on PPIs, based on data from well-controlled randomized trials.[46,47] A consensus panel of the American College of Cardiology Foundation, the American Heart Association, and the ACG said that PPIs may be used for appropriate indications in patients taking clopidogrel.[47]

Hypomagnesemia. By an unknown molecular mechanism, PPIs are thought to reduce intestinal magnesium absorption, leading to hypomagnesemia. A meta-analysis published in 2011 showed that PPI-induced hypomagnesemia is a drug-class effect and occurred after a median of 5.5 years of PPI use. Stopping the PPI resulted in magnesium recovery in 4 days, and rechallenge led to recurrence within 4 days.[48]

Clinically, all PPIs appear to be similar in their symptom relief

Hence, to avoid putting patients on long-term PPI therapy at risk, clinicians should anticipate this problem. Our practice is to check the magnesium level before starting a patient on long-term PPI therapy, and then to repeat the measurement every 1 to 2 years.

Baclofen

Transient lower esophageal sphincter relaxation has been shown to be a cause of reflux in healthy people and in patients with GERD.[49]

Baclofen, a muscle relaxant with selective gamma-aminobutyric acid receptor class B agonist properties, reduces transient lower esophageal sphincter relaxation in humans.[50] In a well-designed, double-blind, randomized controlled trial, baclofen was associated with a significant decrease in upright reflux on 24-hour pH monitoring and significant improvement in belching and overall reflux symptoms.[51] However, baclofen is not approved by the US Food and Drug Administration for the treatment of GERD, and its use may be limited by side effects such as somnolence and dizziness.

Antireflux surgery

Antireflux surgery is a reasonable option for selected patients with chronic GERD. The main types of surgery are laparoscopic fundoplication and, for obese patients, gastric bypass. Reasons to consider antireflux surgery include desire to stop PPI therapy, esophagitis not healed by PPIs, symptomatic hiatal hernia, and refractory reflux documented by pH testing.[41]

In general, surgical therapy may be considered in patients who respond to PPIs, but patients who do not respond to PPIs are less likely to respond to antireflux surgery.[15] Other patients less likely to respond are those with symptoms of dyspepsia, such as nausea, vomiting, and epigastric pain.[41]

Common adverse effects of antireflux surgery include gas-bloat syndrome (up to 85% of patients), dysphagia (10% to 50% of patients), diarrhea (18% to 33% of patients), and recurrent heartburn (10% to 62% of patients).[52]

Endoscopic and minimally invasive antireflux procedures include endoscopic plication of the lower esophageal sphincter, radiofrequency augmentation of the lower esophageal sphincter, and sphincter augmentation by a string of titanium beads. While some have shown promise, they are not recommended by the most recent ACG guidelines, given lack of long-term data.[41]

REFRACTORY GERD

There is no consensus on the definition of refractory GERD. However, for the sake of simplicity, we can define it as persistence of suspected GERD symptoms despite treatment with a PPI. This may vary from a partial response to PPI therapy to a complete absence of response.

It is extremely important to rule out non-GERD causes of the ongoing symptoms, such as achalasia, gastroparesis, eosinophilic esophagitis, rumination, and aerophagia. PPI nonresponders are more likely to be obese, poorly compliant, and have extraesophageal symptoms.[53–56] As previously discussed, PPIs should be taken 30 to 60 minutes before meals. For patients whose symptoms fail to respond to standard-dose daily PPI therapy, switching to another PPI or doubling the dose is common, although data to support this practice are limited. Of note, omeprazole-sodium bicarbonate has been shown to provide more symptom relief in nocturnal GERD.[57] Additionally, adding a nighttime histamine-2 receptor antagonist may also help in patients with objective nighttime reflux.[41]

After noncompliance and suboptimal PPI dosing have been ruled out, PPI nonresponders with typical symptoms should undergo upper endoscopy and subsequent pH monitoring. Normal esophageal acid exposure on pH testing suggests functional heartburn or functional dyspepsia. Negative pH testing in a patient with atypical symptoms suggests a non-GERD cause of symptoms, and referral to an otolaryngologist, pulmonologist, or allergist is often warranted.

While antireflux surgery can be considered for patients with nonacid reflux on impedance testing, it should again be noted that GERD in patients with no response to PPIs is less likely to respond to antireflux surgery.[15]

TAKE-HOME POINTS

- GERD is a common medical condition, affecting up to 40% of US adults at least once monthly.
- GERD can result in a wide variety of symptoms, including typical heartburn and regurgitation as well as atypical symptoms such as cough.
- On the other hand, keep in mind that multiple non-GERD causes of heartburn and regurgitation may exist.
- Testing for GERD includes endoscopy and pH testing as well as functional testing such as esophageal manometry.
- While in most patients GERD will respond to lifestyle changes and antisecretory therapy such as a PPI, careful attention must be given to patients with symptoms refractory to PPI therapy.
- For a subset of patients, antireflux surgery may be a reasonable option, but care must be taken to exclude patients with a lower likelihood of responding to surgery.

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