CME

Managing heartburn and reflux in primary care

Delaney Provenza, MMS, PA-C; Christopher Gillette, PhD; Brian Peacock, MMS, PA-C; Jared Rejeski, MD

ABSTRACT

This article describes an algorithmic approach to caring for patients presenting with heartburn and reflux, including empiric treatment with acid-suppression therapy and a data-driven approach to diagnostic testing. This article also reviews the efficacy and safety profile of the widely available and commonly used proton pump inhibitors. Refining our approach to diagnostic testing can reduce time to diagnosis, better control patients' symptoms, and limit complications of longstanding disease.

Keywords: heartburn, reflux, acid suppression, proton pump inhibitors, GERD, potassium-competitive acid blockers

Learning objectives

- Review current guidelines for the diagnosis and treatment of GERD.
- Explain diagnostic tools available to investigate the causes of heartburn and reflux.
- Discuss evidence-based lifestyle modifications for patients with heartburn and reflux.
- Identify pharmacologic therapies available for treating acid reflux, including PPIs.

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Pyrosis, or heartburn, is one of the most common gastrointestinal (GI) symptoms encountered by primary care providers (PCPs).[1] Heartburn is described as a burning sensation in the substernal region that may radiate from the epigastrium to the neck. Another common symptom is regurgitation, or reflux, which is the sensation of gastric contents effortlessly rising from the stomach toward the mouth.[2] In a survey of more than 70,000 people living in the United States, nearly a third had experienced heartburn and reflux in the past week.[3] A systematic analysis of the global burden of gastroesophageal reflux disease (GERD) estimated an incidence of 3,793 per population of 100,000.[4] Looking further, the global prevalence of heartburn and reflux in adolescents and adults is about 15%.[5]

Many people experience heartburn and reflux at some point in their lives, but the presence of these symptoms alone is not sufficient to make a diagnosis of GERD. According to the American College of Gastroenterology (ACG), GERD is "a condition in which the reflux of gastric contents into the esophagus results in symptoms and/or complications" such as erosive esophagitis and Barrett esophagus.[2] Although a symptom-based diagnosis of GERD may be quick and cost-effective, it has shown limited sensitivity and specificity when made by PCPs (63%, 63%) and gastroenterologists (67%, 70%), even when taking into consideration the response to proton pump inhibitors (PPIs).[6,7] The presence of heartburn and reflux does not distinguish patients with disease complications from those with nonerosive reflux disease, nor can these symptoms distinguish GERD from other causes such as functional heartburn, reflux hypersensitivity, or eosinophilic esophagitis.[2,7] Therefore, diagnostic testing may be necessary to confirm the correct diagnosis and treatment.

The symptoms of GERD typically can be controlled using a combination of lifestyle modifications and drug therapy. Many first-line medications used to treat GERD are now available over the counter, yet morbidity from GERD

At Wake Forest University School of Medicine in Winston-Salem, N.C., **Delaney Provenza** is an assistant professor, **Christopher Gillette** is an associate professor and director of research and scholarship, **Brian Peacock** is an assistant professor and PA program director, and **Jared Rejeski** is an assistant professor of gastroenterology. The authors have disclosed no potential conflicts of interest, financial or otherwise.

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Key points

- The diagnosis of GERD is based on symptoms, response to therapy, endoscopic features, and pH monitoring.
- Patients with heartburn or reflux without alarm features should undergo an 8-week trial of treatment with PPIs to assess response, with an attempt to deprescribe after 8 weeks in patients whose symptoms resolve.
- Patients with heartburn in the presence of dysphagia, vomiting, hematemesis, melena, or unintentional weight loss should be referred for EGD.
- PPIs are safe, effective, and the gold-standard therapy for patients with GERD.

remains substantial. Direct and societal costs to treat GERD and its associated complications are also high. In 2016, an estimated 4.6 million healthcare visits were related to heartburn, and in 2018, $12 billion in healthcare costs were associated with esophageal disease.[1]

This article provides an algorithmic, evidence-based approach to caring for patients with heartburn and reflux using the most updated guidelines available. This article also reviews the safety and efficacy of the widely available and commonly used PPIs. Refining the approach to GERD by improving diagnosis and treatment is essential to improve quality of life, reduce healthcare costs, and prevent long-term complications for patients affected by this condition.

DIAGNOSIS

GERD often is diagnosed clinically based on hallmark symptoms and the patient's response to medication therapy. However, diagnostic testing is indicated and is important for certain groups, such as patients with alarm symptoms, those at increased risk for complications, those with unusual clinical presentations, those with poor response to therapy, and those for whom uncertainty remains around the diagnosis.

No single test is the gold standard for diagnosis of GERD. Rather, diagnosis is based on a combination of symptoms, response to therapeutic intervention, endoscopic findings, and reflux monitoring (**Table 1**).[2] Guidelines published by the American Gastroenterological Association and the ACG provide an algorithmic approach to diagnostic testing that helps to balance the efficient and cost-effective clinical diagnosis with a more objective approach (**Figure 1**).[2,8]

Symptom-based diagnosis Patients presenting with persistent and bothersome heartburn and reflux with no alarm features (dysphagia, vomiting, hematemesis, melena, or unintentional weight loss) are appropriate for a trial of lifestyle modifications and an 8-week trial of a PPI at the standard prescription dosing.[2] Those who respond to lifestyle modifications and a PPI trial are likely to have GERD.[2] However, a recent study found that up to half of patients with symptoms of heartburn and reflux have ongoing symptoms despite daily PPI use.[3] When patients with heartburn and reflux do not respond to a PPI trial, or when symptoms return and persist after discontinuing medical therapy, pursue diagnostic testing to confirm or refute the diagnosis of GERD.[2,8] GERD has significant symptom overlap with other GI disorders, and symptom-based diagnosis is limited in sensitivity and specificity.[6,7] Clinicians who suspect that a patient requires additional diagnostic workup for their symptoms should refer the patient to gastroenterology.

Endoscopy The first-line diagnostic test for patients experiencing alarm symptoms or refractory heartburn and reflux is a diagnostic esophagogastroduodenoscopy (EGD).[2,7] EGD is the initial diagnostic test of choice because it allows for direct inspection of the esophageal and gastric mucosa for objective evidence of GERD, such as erosive esophagitis or Barrett esophagus.[2,8] Erosive esophagitis is inflammation or erosion of the distal esophageal mucosa as a result of repeated exposure to gastric acid. In Barrett esophagus, also called Barrett metaplasia, the normal squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium.[2] Advanced erosive esophagitis and Barrett metaplasia are considered diagnostic for GERD (**Table 1**).[2,8] Additional complications of long-term acid exposure are Schatzki rings and esophageal stricture, both of which narrow the esophageal lumen and can be identified on EGD.[8] EGD also can identify the presence of a hiatal hernia, a mechanical factor that can promote pathologic esophageal reflux.[9] A 2021 study reported a significant difference in hiatal hernia surface area between patients with and without GERD, with larger hiatal hernias being associated with the presence of GERD.[9]

The initial EGD should be performed when the patient has been off the PPI for 2 to 4 weeks because PPI therapy can mask esophagitis and impede GERD diagnosis.[2,8] PPI therapy also can cause false-negative biopsies for eosinophilic esophagitis, a condition that should be evaluated on initial EGD if the patient is experiencing dysphagia.[10]

TABLE 1. Diagnostic criteria for GERD[2,8,11]

Diagnosis is based on a combination of symptoms, response to therapeutic intervention, endoscopic findings, and reflux monitoring.

Symptoms
- Heartburn and/or reflux that impairs patient quality of life

Endoscopic findings
- Los Angeles grade B, C, or D esophagitis (used by endoscopists to stratify the severity of esophagitis based on appearance)
- Barrett metaplasia (greater than 3 cm)

Reflux monitoring
- Abnormal esophageal acid exposure

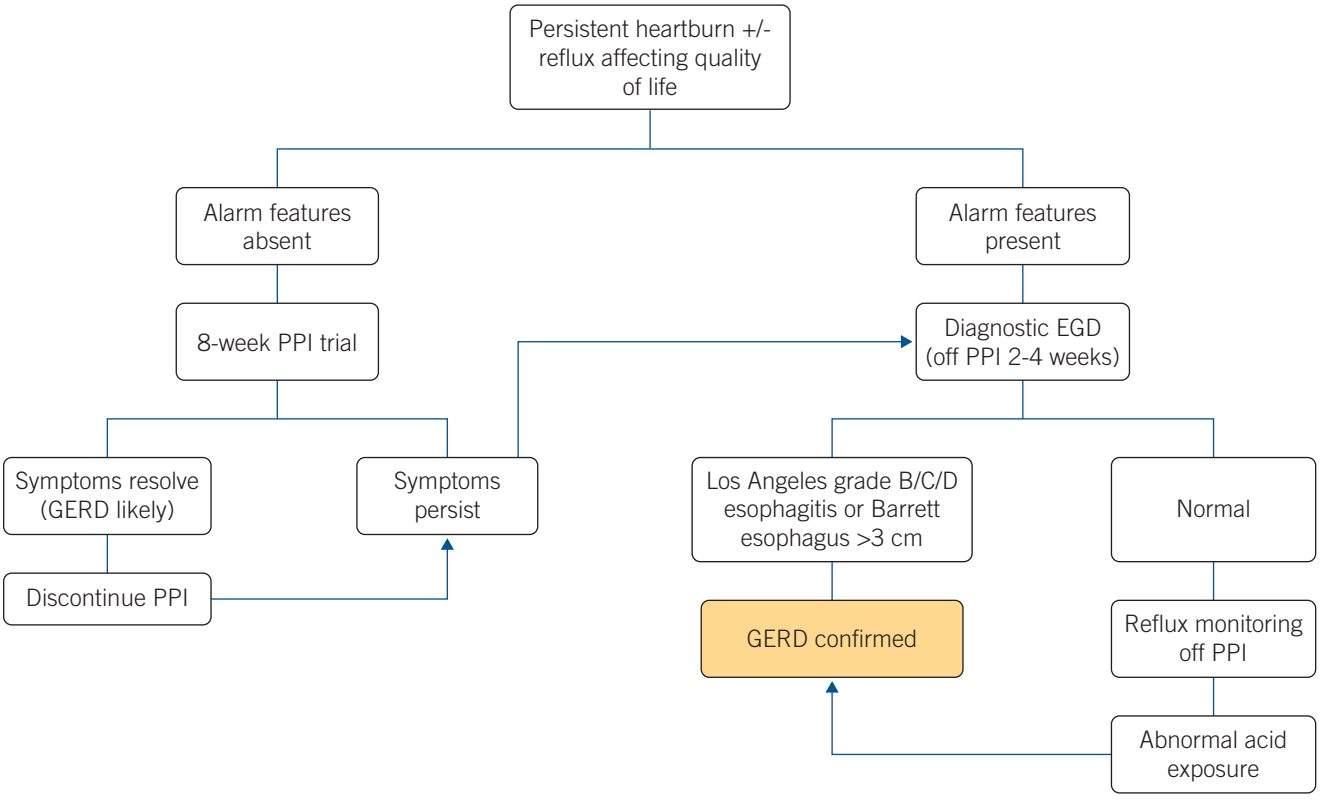

FIGURE 1. Approach to the diagnosis of GERD[2,8]

Although PPIs should be avoided during this timeframe, antacids can be used for symptom control.[2]

Although EGD can identify changes in the esophagus such as esophagitis, up to 80% of patients who undergo endoscopic evaluation for uncomplicated heartburn and reflux will have a normal examination.[11] Therefore, patients with PPI-refractory heartburn and reflux with normal EGD should undergo additional testing to confirm or rule out the diagnosis of GERD.[2,8,11]

Reflux monitoring Data collected for reflux monitoring include acid exposure time, number of reflux events, and symptom correlation.[2,12] The two main methods of reflux monitoring are via a wireless telemetry capsule or a transnasal catheter. The wireless telemetry capsule is endoscopically attached to the esophageal mucosa, and data monitoring lasts from 48 to 96 hours.[2] Transnasal catheters can perform pH and impedance testing, measuring acidic and nonacidic reflux events. Transnasal catheters typically are worn for 24 hours before removal.[2,12] Reflux monitoring is ordered and interpreted by gastroenterology.

Patients who have not had confirmation of diagnosis based on endoscopic findings (erosive esophagitis or Barrett esophagus) should undergo reflux monitoring while off acid-suppression therapy to confirm or refute the diagnosis of GERD.[11,12] In this case, stop PPI therapy 7 days before reflux monitoring.[11,12] GERD can be diagnosed based on abnormal esophageal acid exposure.

Reflux monitoring can differentiate patients with increased esophageal acid exposure who meet criteria for GERD from those with reflux hypersensitivity (no pathologic increase in acid exposure, but symptom correlation to reflux events) or functional heartburn.[11,12] Also consider this diagnostic methodology for patients with atypical (or extraesophageal) symptoms of GERD, because pH monitoring also can indicate whether atypical symptoms such as chronic cough truly correlate with acid reflux events or whether evaluation and testing for alternative diagnoses are needed.[2,12]

Patients with a confirmed diagnosis of GERD with ongoing symptoms despite maximum PPI therapy may undergo pH monitoring while on acid-suppression therapy to see if pathologic reflux remains and, if so, determine whether reflux events correlate with the patient's ongoing symptoms.[11,12]

TREATMENT

The symptoms of GERD typically can be controlled using lifestyle modifications and pharmacologic therapy.

Lifestyle modifications Several lifestyle modifications should be recommended for patients experiencing heartburn and reflux.[8] Some of these interventions are thought to be effective because they reduce intra-abdominal pressure, thus decreasing gastroesophageal reflux. Weight loss has been associated with improvement in heartburn and reflux

symptoms in patients who are overweight or have obesity.[13] Patients should also be advised to avoid consuming meals within 2 to 3 hours of bedtime or lying flat.[13] For those who struggle with nocturnal symptoms, elevating the head of the bed at least 6 inches (15.2 cm) or using a mattress wedge has been demonstrated to reduce GERD symptoms and esophageal acid exposure.[13] Patients also may have symptom improvement with lying left-side down, because lying right-side down results in anatomic positioning that favors reflux.[2]

Though suboptimal data support this, smoking cessation and avoidance of trigger foods also have demonstrated improvement in symptoms of heartburn and reflux.[2] Many patients who experience heartburn and reflux cite trigger foods, most commonly coffee, carbonated beverages, citrus, spicy foods, and tomato-based products.[2] Although these foods have not been shown to increase esophageal acid exposure, their correlation with symptoms may be driven by mechanism of direct irritation rather than exacerbating gastroesophageal reflux.[2] Therefore, advise patients to monitor their response to reduction in trigger foods and avoid them accordingly.

Pharmacologic therapy PPIs are an evidence-based standard of treatment for patients with persistent heartburn and reflux.[2,8] PPIs inhibit the ATPase enzyme that transports hydrogen ions into the gastric lumen, thus reducing intragastric acid.[14] PPIs should be dosed 30 to 60 minutes before the first meal of the day, because they are prodrugs that require activation in an acidic environment for maximal effect.[14]

Data demonstrate superior control of symptoms as well as improved healing of mucosal damage compared with histamine-2 receptor antagonists (H2RAs).[15,16] However, patients with mild or infrequent symptoms of heartburn and reflux can use as-needed therapy with over-the-counter antacids or H2RAs if these are effective at controlling their symptoms.[12]

Patients with persistent and bothersome heartburn and reflux in the absence of alarm symptoms should be prescribed an 8-week trial of a PPI at standard dosing.[2,3] If a patient's symptoms have not resolved on PPI, assess adherence to the prescribed regimen and reassess the diagnosis.[2,12] Pursue diagnostic testing to confirm a diagnosis of GERD if needed.[2,3,12]

Optimizing therapy For patients with GERD who adhere to daily PPI therapy and have rare breakthrough symptoms, consider on-demand antacid therapy. For those with persistent breakthrough symptoms, a PPI dose increase or change to a different PPI is recommended.[2,8] In a study of patients with persistent heartburn despite once-daily PPI use, randomization to twice-daily use of a PPI of the same formulation and once-daily dosing of a different formulation of PPI were both equally effective at controlling symptoms, although there was no objective measure of reflux with pH monitoring.[17] Twice-daily dosing of PPI has superior acid suppression on pH monitoring compared with once-daily dosing.[18] When a PPI is dosed twice daily, the medication should be taken 30 to 60 minutes before breakfast and before dinner, rather than before bedtime.[17]

Patients with a confirmed diagnosis of GERD and persistent symptoms despite twice-daily PPI dosing are considered to have refractory GERD.[2] In this case, an H2RA, such as famotidine, may be added on an as-needed basis before bedtime for patients with nocturnal symptoms.[8] When adding an H2RA, as-needed dosing is recommended because loss of pH control (tachyphylaxis) appears to occur after about 1 month of scheduled bedtime dosing.[19] Patients with refractory GERD are best suited for consultation with gastroenterology to consider further diagnostic testing and alternative therapies. Endoscopic and surgical options such as laparoscopic fundoplication or magnetic sphincter augmentation may be appropriate for select patients.[8] However, twice-daily PPI dosing is not approved by the FDA for treating GERD. Further, limited evidence shows that a double dose of a PPI is effective only for 2 to 3 months for a subset of patients.[20] Patients who are on long-term PPIs might benefit from a symptom review and potential deprescribing (dose reduction or tapering to discontinuation).[21]

Meta-analyses have not demonstrated clinically meaningful differences in symptom control, esophageal pH measurement, or esophagitis healing rates among various PPIs.[18,22] In clinical practice, the selection of a PPI therefore should be based on consideration of safety, tolerability, affordability, and simplicity of use.[12] For patients with prescription insurance, a review of preferred medications and nonpreferred formulations may be helpful.

The FDA recently approved vonoprazan, a potassium-competitive acid blocker for the healing and maintenance of healing of all grades of erosive esophagitis and relief of heartburn associated with erosive GERD in adults. Additionally, it can be used in combination with amoxicillin or amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* infection in adults.[23]

De-escalating therapy PCPs must know who is appropriate for de-escalation and who should receive chronic maintenance dosing of PPI. Patients with complications of GERD, including severe erosive esophagitis, Barrett esophagus, or esophageal stricture, should remain on chronic (indefinite) acid-suppression therapy.[5] When a patient is found to have erosive esophagitis, treatment with an 8-week course of twice-daily PPI is recommended, followed by repeat endoscopy to assess for mucosal healing.[2] Once the mucosa has healed, PPI dosing may be reduced to once daily, but at least once-daily dosing of a PPI is recommended.[2,5] Other patients who may require long-term PPI use include those with eosinophilic esophagitis, those with Zollinger-Ellison syndrome, or

those who are at high risk for or suffer from recurrent upper GI bleeding.[5]

Patients with uncomplicated or nonerosive GERD do not require daily maintenance therapy.[5] In this group, an attempt should be made to discontinue PPIs or switch to on-demand therapy, using an evidence-based deprescribing strategy to minimize the risk of symptom recurrence.[2,24] Those with persistent symptoms lasting more than 2 months while off PPI therapy should be considered for reinitiating daily scheduled PPI therapy.[5] For those with confirmed nonerosive reflux disease who require daily therapy for symptom control, an attempt should be made to de-escalate therapy to the lowest effective dose that provides adequate control of symptoms, and the necessity of ongoing PPI use should be reassessed annually.[5,25]

> Reassess the need for PPI therapy every 6 to 12 months.

Some clinicians remain wary of abrupt discontinuation of PPIs because of potential rebound acid hypersecretion that could exacerbate symptoms, and patients certainly should be counseled about this possibility.[5] However, no strong evidence exists to suggest that this mechanism results in a true exacerbation of symptoms.[2] Stepwise dose reduction or abrupt discontinuation are considered appropriate methods for de-escalation.[5] Have a plan for managing symptom recurrence, such as telling patients that the PPI can be restarted if symptoms return.[24] Another practical approach would be to de-escalate therapy to an H2RA once daily and then to on-demand therapy as patients are able.[2,5]

SAFETY OF LONG-TERM PPI THERAPY

PPIs are a standard treatment for GERD and related disorders and are widely prescribed in primary care and gastroenterology.[25] Over the past 2 decades, the long-term safety profile of these medications has been scrutinized. Most concerns are based on observational studies that note associations between long-term PPI use and cardiovascular events, chronic kidney disease, enteric infection including *Clostridioides difficile*, small intestinal bacterial overgrowth, pneumonia, dementia, osteoporotic bone fractures, gastric cancer, and deficiencies in micronutrients such as vitamin B12 and magnesium.[2,25] These potential risks may be related to the underlying mechanism of gastric acid suppression. For example, gastric acid is a natural defense against ingested pathogens; suppressing gastric acid release may decrease the body's natural defenses to GI infections.[2] Other risks have been proposed based on routes of drug metabolism. Omeprazole is an inhibitor of CYP2C19, the enzyme that activates clopidogrel, so the use of these drugs together could reduce clopidogrel concentrations and increase cardiovascular events in some patients.[2] However, randomized trial data suggest that these relationships are not causal and can likely be attributed to residual confounding factors.[26] A recent study by Moayyedi and colleagues found that 17,598 patients age 65 years or older randomized to pantoprazole 40 mg daily or placebo had no significant differences in complications over 3 years, except for the PPI group having higher rates of non-*C. difficile* enteric infections.[26]

Despite strong data supporting the safety and efficacy of PPIs, clinicians remain wary about the long-term use of these medications. In a survey of more than 430 internal medicine physicians, 70% responded that they were somewhat concerned or very concerned about adverse reactions to PPIs.[27] Clinicians seem to underestimate the efficacy of PPIs and overestimate the likelihood of their adverse reactions, and most respondents admitted to changing their prescribing patterns based on concerns about PPIs. In a clinical scenario involving prevention of high-risk upper GI bleeding, nearly 80% of clinicians inappropriately recommended discontinuation of a long-term PPI in a patient, despite guideline recommendations.

Overall, long-term use of PPIs appears to generally be safe, and when prescribed appropriately, the benefits outweigh risks.[2,5] However, a best practice to support appropriate prescribing is to reassess the need for PPI therapy every 6 to 12 months.[5] Practical advice exists for prescribing PPIs when there is concern for adverse reactions, such as in patients taking clopidogrel or those with renal insufficiency. The 2014 American Heart Association/American Stroke Association guidelines for the prevention of stroke recommend using PPIs that are less potent inhibitors of CYP2C19 (such as pantoprazole) in patients taking clopidogrel.[28] Patients with reduced kidney function requiring long-term PPI use should undergo routine monitoring of kidney function with serum creatinine every 3 to 6 months, based on the severity of their disease and the Kidney Disease: Improving Global Outcomes clinical practice guideline on managing BP in patients with chronic kidney disease.[2,29]

CONCLUSION

Heartburn and reflux are among the most common GI complaints encountered by PCPs.[1] No single test is recommended for diagnosing GERD. Rather, diagnosis is based on a combination of reported symptoms, response to therapeutic interventions, endoscopic findings, and pH monitoring.[2,8] A data-driven algorithmic

approach can be used to determine appropriate candidates for empiric therapy and which patients require diagnostic testing for accurate diagnosis.[2,8] Patients with persistent and bothersome heartburn and reflux without alarm features should undergo an 8-week trial of PPI therapy and lifestyle modifications.[2] Diagnostic testing such as EGD should be reserved for those who are experiencing alarm features or when symptoms are not adequately controlled despite PPI therapy.[2,8] In appropriately selected patients, PPIs are a proven, recommended intervention, and appropriate long-term use appears safe and cost-effective.[2,5,25,26] Refining the approach to diagnostic testing can reduce time to diagnosis, better control symptoms, and limit complications of longstanding disease. **JAAPA**

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