Gastroesophageal Reflux Disease: Clinical Features and Management for the Primary Care Physician

Case Studies and Commentary, Brian W. Behm, MD, MS, and David A. Peura, MD

Abstract

- **Objective:** To provide an overview of the clinical features, diagnosis, and medical management of gastroesophageal reflux disease (GERD).
- **Methods:** Review of recent literature relating to epidemiology, diagnosis, and management of GERD.
- **Results:** GERD is a common condition that results from reflux of gastric contents into the esophagus, leading to bothersome symptoms or complications such as esophagitis or Barrett’s esophagus. It can impact quality of life and productivity at home and in the workplace. Several factors, including the epidemic of obesity, are fueling the rising incidence of GERD in the United States. Diagnosis of GERD can reliably be made based on fairly specific clinical symptoms and response to acid suppressive medication. Proton pump inhibitors (PPIs) are the gold standard for GERD treatment, but they have inherent dosing limitations that can influence their effectiveness. Once symptoms are controlled, medication should generally be tapered and decreased to the lowest dose and dosing interval that controls symptoms, barring complicated GERD. Avoiding high-dose chronic PPI treatment whenever possible may mitigate some of the adverse effects associated with acid suppression. Persistent, longstanding, severe, or poorly controlled symptoms, especially if they occur at night, should prompt one-time endoscopy to evaluate for esophagitis and alternative causes of symptoms.
- **Conclusion:** In most instances, a reliable diagnosis of GERD can be made based on typical presenting symptoms and response to empiric acid suppressive medication. Medical management can control symptoms and improve the quality of life in most GERD patients.

Gastroesophageal reflux disease (GERD), a chronic condition that affects more than 18 million Americans, is characterized by retrograde movement of gastric contents into the esophagus that is associated with troublesome symptoms and/or complications [1]. Physiologic reasons for GERD include increased episodes of transient lower esophageal sphincter relaxation, reduced lower esophageal sphincter pressure, and impaired or ineffective esophageal motility [2]. The number of GERD sufferers is steadily increasing, and obesity, diet, and lifestyle are among the factors that appear to be responsible for its increasing prevalence [3–5]. While heartburn and regurgitation are the 2 most specific symptoms of GERD, less typical and less specific symptoms such as hoarseness, cough, wheezing, and globus can also occasionally be caused by acid reflux [6,7]. GERD-related symptoms, especially when occurring at night, can impair quality of life and affect productivity at home and at work [8]. The annual economic burden imposed by GERD includes direct costs of more than $9 billion for consultation, testing, and treatment as well as indirect costs of $75 billion due to absenteeism and presenteeism in the workplace [8,9]. In fact, the American Gastroenterological Association’s burden of disease survey found that GERD was the single most expensive digestive disease condition in the United States [9].

Treatment for GERD includes lifestyle advice such as weight reduction, avoiding large or late meals, and elevating the head of the bed, along with medication to suppress acid secretion. Treatment is generally effective in controlling symptoms [6,7,10]. Medications typically used to treat GERD include the histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) [11,12]. H2RAs are more effective than placebo and work quickly to control symptoms, but their use is limited by their short duration of action (< 12 hours) and tachyphylaxis that
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develops during chronic continuous administration [13]. The H2RAs are ideally suited for periodic treatment of occasional or meal-provoked heartburn, and they can be used at bedtime, but only short term, in conjunction with PPIs to control nighttime GERD symptoms [14]. PPIs work more slowly than H2RAs but their duration of action is longer (> 24 hours). Comparative studies have shown that PPIs are superior to H2RAs for both short- and long-term treatment of reflux-related symptoms and mucosal damage when it is present [11,12,15]. As such, they are considered the gold standard for management of GERD.

PPIs do have some pharmacologic limitations that can influence their effectiveness. For example, they irreversibly inhibit proton pumps on the acid-producing parietal cells in the stomach. This inhibition is only possible if the pumps are activated by food. Since the kinetic half-life of PPIs is 1 to 2 hours, the drugs must be dosed prior to a meal or they lose effectiveness [16]. This can be a major problem for patients who take their medication in the morning and do not regularly eat breakfast. Improper meal-associated dosing is a common reason for PPI failure. Also, new pumps are regenerated throughout the day, and dormant pumps can become active with subsequent meals [16]. Therefore, patients who eat large meals in the evening, especially just before going to bed, times when there is no longer any PPI left to inhibit newly activated or synthesized proton pumps, are subject to breakthrough symptoms. Newer-generation PPIs currently available (dual delayed-release dexlansoprazole) or under FDA review (extended-release rabeprazole) attempt to address these pharmacologic limitations. By incorporating delayed- or extended-release technologies, they prolong effective plasma concentration of drug and eliminate the need to dose medication just prior to a meal [17]. Since all available PPIs appear to be effective in healing esophagitis and controlling GERD symptoms, selecting a particular drug within the PPI class is generally based on cost (several generic and OTC formulations are available), formulary availability, and prescriber or patient preference.

Most GERD patients have uncomplicated disease, but some will develop severe esophageal mucosal injury or Barrett’s esophagus, a potentially premalignant condition in which the esophageal squamous lining is replaced by specialized intestinal metaplasia. The incidence of Barrett’s esophagus in patients with GERD is approximately 10% [18,19]. If Barrett’s esophagus is found, periodic surveillance endoscopy with biopsy is recommended to detect dysplasia or cancer in an early and potentially curative stage [20], although the effectiveness of surveillance in reducing overall esophageal cancer mortality remains controversial [21,22]. Endoscopic mucosal resection and/or ablation have become less morbid alternatives to esophagectomy in Barrett’s esophagus complicated by high-grade dysplasia or T1 mucosal cancer [23]. Studies are also underway to determine the long-term benefit of ablation of low-grade dysplasia and nondysplastic Barrett’s epithelium. Pending results from such studies, endoscopic ablation should currently be reserved for patients with dysplasia or early cancer.

A clinical diagnosis of GERD can be reliably made in individuals who present with heartburn (rising retrosternal discomfort or burning worsened by meals or when reclining and eased by antacids) and/or regurgitation (perception of flow of refluxed stomach contents into the mouth or throat) [1,24]. The diagnosis of GERD is further supported by symptom response to several weeks of empiric acid suppression, the so-called “PPI test” [7,24]. Less typical and less specific symptoms such as hoarseness, cough, wheezing, and globus can also occasionally be caused by acid reflux [24]. Concomitant heartburn and/or regurgitation occurring along with these less typical symptoms increases the likelihood they are GERD related [7]. Lack of these typical symptoms should raise suspicion of a non-GERD problem. While heartburn usually resolves within several weeks of empiric treatment, these less typical symptoms may require several months of high-dose PPI treatment before symptom improvement is seen. In many cases, symptom improvement and not total resolution is seen.

CASE STUDIES
Initial Presentation

Case 1

A 57-year-old man presents for evaluation of reflux. He reports a history of intermittent heartburn and regurgitation occurring a few times per week for the past 10 years. His symptoms initially improved with over-the-counter antacids and intermittent use of H2RAs. However, he has developed worsening symptoms over the past 3 years, with daily symptoms particularly after meals and at night. Three months ago he began taking an over-the-counter PPI (omeprazole 20 mg) but has had persistent symptoms on this medication. He has tried elevating the head of his bed and avoidance of eating before going to bed without significant improvement.

Case 2

A 48-year-old woman presents with a 6-month history of chest discomfort that has been attributed to
reflux. Her symptoms have been poorly controlled with H2RAs and PPI therapy. She has been tried on several different PPIs including trials of twice daily (before breakfast and before dinner) PPI therapy with incomplete relief of symptoms. Her symptoms include aching chest pain sometimes made worse by large meals but her symptoms can occur any time of day. She has frequent nighttime chest discomfort. Her symptoms have been causing sleep disturbances. This, coupled with frequent daytime symptoms, is causing increased anxiety and difficulty concentrating at work. She misses work once or twice per month because of her symptoms.

**Additional History and Physical Examination**

**Case 1**

On further questioning, the patient takes omeprazole at bedtime because his most bothersome symptoms occur at night. He does not have any associated dysphagia, odynophagia, vomiting, or weight loss. He denies any associated shortness of breath, wheezing, voice changes, sore throat, nocturnal cough, or chest pain. His other medical problems include diet-controlled hypertension and obesity. He drinks alcohol typically twice per week and does not smoke. He rarely eats breakfast—just coffee—and although he does not eat just before bedtime, at least twice per week he eats a late evening meal with business colleagues that he thinks might be the times his nighttime symptoms are worse. He is taking no medications other than the omeprazole and occasional antacids for breakthrough symptoms. He has a brother with GERD and diabetes and his father had colon polyps diagnosed at age 70. On examination, his heart and lungs are unremarkable and he has no abdominal tenderness and no palpable masses. His body mass index is 31. Laboratory data includes a normal complete blood count without evidence of anemia.

**Case 2**

This patient reports mild dysphagia, typically with solid foods and occasionally liquids, which has remained stable over the past year. She does not report any associated weight loss, odynophagia, or vomiting. She reports some hoarseness when she wakes up in the morning but does not have any associated cough or sore throat. She is currently taking lansoprazole 30 mg 30 minutes prior to breakfast and dinner, ranitidine 300 mg at bedtime, and is using antacid medications several times per day with incomplete relief. On examination, the patient is a healthy-appearing, thin Caucasian female. Oropharyngeal exam is normal, heart and lungs are unremarkable, and her abdominal exam is benign without associated masses. Laboratory data includes a normal complete blood count without evidence of anemia.

- **What is the role of diagnostic testing in patients with suspected GERD?**

GERD can usually be diagnosed on the basis of symptoms without additional diagnostic testing [7,10,24]. Reflux symptoms that are troublesome to the patient constitute “disease” and do require treatment. In the absence of alarm symptoms, patients should first be treated empirically with antisecretory therapy, usually once-daily PPI. Upper endoscopy may be considered for patients with severe or refractory symptoms, patients with alarm symptoms (ie, dysphagia, odynophagia, vomiting, gastrointestinal bleeding or iron-deficiency anemia, unintentional weight loss, or upper abdominal mass), and for assessing risk of complications, including the identification of Barrett’s esophagus and esophageal cancer [7,10,24]. However, it should be noted that the correlation between the severity of GERD symptoms and endoscopic findings is poor and the majority of patients with GERD symptoms will have a normal endoscopy [1,24,25]. Because of this, the suggestion that only patients with documentable esophagitis should have access to chronic PPI therapy is not supportable, as patients without visible mucosal damage may also have symptoms due to pathologic acid reflux that may not be adequately controlled with alternative therapy [7]. Also, symptom severity and effect on quality of life are generally comparable in GERD sufferers with or without esophagitis [26]. Endoscopy with biopsy also allows the diagnosis of conditions such as infectious or eosinophilic esophagitis that can on occasion mimic GERD [27]. Therefore, patients who undergo endoscopy to evaluate symptoms poorly responsive to PPIs, especially those with complaints of dysphagia, should have esophageal biopsies taken at several levels of the esophagus to exclude eosinophilic esophagitis even if the typical endoscopic findings of the condition are absent [7,27].

**Additional Diagnostic Tests**

Additional tests for esophageal reflux, including esophageal pH monitoring, usually do not outperform symptom-based diagnosis [7,10,24] but may be helpful in select cases. Esophageal pH monitoring may be helpful in patients with persistent symptoms in whom a trial of acid suppression has failed, and it remains the best method to study the actual amount of reflux occurring and period of the reflux (upright, supine or combined) in a particular patient. It is also the best method for assessing the associa-
testing would generally not be required. His symptoms do not suggest a cardiac etiology, but this should always be considered when clinically appropriate. In this setting, a trial of empiric acid suppressive therapy would be a correct initial approach. Antisecretory therapy may be both diagnostic and therapeutic. Lifestyle modifications can be used instead of antisecretory therapy in patients with mild occasional symptoms and can be used as an adjunct to antisecretory therapy in those with more frequent troublesome symptoms (Table 1). Specific recommendations, including avoiding specific foods, late meals, and certain activities, should be tailored to the individual circumstances of the patient [6,10]. Weight loss should be advised for overweight individuals [6]. Elevation of the head of the bed should be considered for patients with recumbent or nocturnal heartburn [6]. In general, endoscopy is not necessary in the patient who presents with typical symptoms and uncomplicated disease [6,10]. Endoscopy may be indicated in those patients with symptoms suggesting complicated disease or those patients at risk for Barrett’s esophagus (Table 2) [34–37]. Even though this patient has typical reflux symptoms, based on his age, gender, obesity, symptom duration (10 years), and timing (nocturnal), he should undergo a one-time endoscopy to exclude Barrett’s esophagus [30]. At the same time, based on age he should undergo colorectal cancer screening with colonoscopy if it has not previously been performed [38].

**Case 2**

This patient has had a poor response to antisecretory therapy and reports intermittent solid and liquid dysphagia. The most frequent causes of a poor response to PPI therapy include nonadherence or incorrect dosing of PPI or non-GERD causes of symptoms (Table 3). True PPI “refractoriness” with inadequate acid suppression is rare with proper dosing, especially when the drug is given twice daily. Factors that might play a role in this patient’s symptoms include nonesophageal causes of chest pain, including musculoskeletal and cardiac etiologies; because cardiac disease is always a possibility, it is important to exclude this in patients at risk for cardiovascular disease. There is heart in heartburn for a reason! Esophageal causes for her symptoms could include functional heartburn, incomplete acid suppression or acid breakthrough, bile or nonacid reflux, or eosinophilic esophagitis. Improper dosing or nonadherence with PPI therapy among nonresponders is common, so it must be considered and specifically queried [39,40]. Esophageal dysmotility disorders may also be associated with reflux symptoms, and delayed gastric emptying may increase the risk of breakthrough reflux symptoms as well. Although upper endoscopy is commonly performed in this clinical scenario, it often does not identify pathology that changes management of the patient’s symptoms [6,24]. In
this patient, if cardiac etiologies have been excluded, an esophagogastroduodenoscopy with esophageal biopsies to exclude eosinophilic esophagitis and a 24-hour ambulatory pH monitor off of PPI therapy to confirm a diagnosis of GERD would be reasonable.

**Treatment and Course**

**Case 1**

The patient was taking his PPI therapy inappropriately at bedtime, a fairly common cause of persistent GERD symptoms on PPI therapy. His upper endoscopy was normal (no evidence of Barrett’s esophagus and biopsies showed no evidence of eosinophilic esophagitis). At colonoscopy he was found to have 4 tubular adenomatous polyps all less than 1 cm; based on current guidelines it was recommended that he repeat his examination in 3 years [38]. To manage his GERD, he was asked to change omeprazole dosing to 30 minutes before dinner since he does not regularly eat breakfast. Weight loss was also encouraged. After 2 weeks he noted significant improvement in his symptoms, and since he did not have evidence of erosive esophagitis, after 8 weeks he switched to on-demand PPI therapy and reported continued satisfaction with his symptom control [41]. He was also advised he could take an H2RA prior to bedtime on those nights when he ate a late evening meal. Had this patient not improved with correct once-daily dosing of PPI, increasing to twice daily PPI would be appropriate before deeming him to be a PPI nonresponder [42] (Figure).

**Case 2**

The patient underwent cardiology evaluation, including stress testing, which showed no evidence of cardiac abnormalities. Upper endoscopy was performed, which was normal. Esophageal biopsies were obtained and showed no evidence of eosinophilic esophagitis. Motility studies were also normal. The patient underwent ambulatory pH monitoring off antisecretory therapy, which showed normal esophageal acid exposure, and the patient’s symptoms did not correlate with acid reflux events. The patient was diagnosed with functional chest pain, her PPI and H2RA were discontinued, and she was given a trial of tricyclic therapy with amitriptyline 25 mg gradually increased to 75 mg at night [43]. At the time of follow up 8 weeks later, the patient reported significant improvement in her symptoms.

**What are the potential consequences of long-term acid suppression?**

PPIs are used by millions of patients with acid-related disorders, which attests to their general safety, tolerability, and effectiveness. However, during the past several years, much has been written about potential long-term risks of PPI use. Most of the reports stem from cohort or case-control analyses, and some are confounded by channeling or variable bias. There are 3 potential issues we will address here. First, while controversial, there does appear to be an association between long-term, high-dose PPI use and an increased risk of fractures [44,45]. In fact, the FDA recently required a fracture warning label for all over-the-counter and prescription PPIs. The mechanism of this fracture risk is not known, since calcium absorption appears adequate in PPI users [46] and PPI users do not appear to have accelerated osteoporosis [47]. PPIs can directly affect osteoclasts, thereby altering bone metabolism, but the clinical significance of this has yet to be proven [48]. Since the association with fractures appears to be dose and duration related, PPIs should generally be used at the lowest dose and dosing frequency necessary to control symptoms. In patients with symptomatic GERD but without erosive esophagitis or Barrett’s esophagus, a trial of step-down therapy to H2 blockers could also be considered.

An increased risk of infections, particularly enteric infections, is a second concern that has been voiced regarding chronic acid suppression [49,50]. Stomach acid is thought to play a major role in preventing colonization and spread of ingested bacteria. PPI users, especially young children,
appear to be at increased risk of infectious gastroenteritis [49,51,52]. In addition, risk for *Clostridium difficile* infection in the community and hospital setting appears to be greater in PPI users [49]. Counseling PPI users about good hygienic practice with emphasis on hand washing with soap and water as well as safe food handling should be routine. As is the case with fractures, PPIs should generally be used at the lowest dose and dosing frequency for the shortest duration necessary to control symptoms.

A third concern related to PPIs is the potential for drug interactions, and the recent FDA warning related to concomitant use of omeprazole and esomeprazole with clopidigrel underscores this concern. Clopidigrel is a prodrug that requires activation by the hepatic CYP2C19 enzyme system to achieve its antiplatelet activity. Since all PPIs are metabolized to a variable degree by CYP2C19 (only omeprazole and esomeprazole appear to actually inhibit the enzyme), there is the potential for interactions that may reduce clopidigrel activation [53]. While some studies have suggested a potential increase in cardiovascular events associated with concomitant PPI use and clopidogrel, the clinical significance of any potential interaction remains controversial [54,55], and more recent high-quality studies have not shown a clinically significant interaction [56,57]. Pending results of these studies, it is best to reassess the concomitant need for PPIs and clopidigrel. If both are clinically necessary, until conclusive evidence of safety has been established, one reasonable option would be to use a PPI other than omeprazole or esomeprazole, with dosing of the PPI and clopidigrel separated by a number of hours.

**What is the role of surgery in GERD?**

Antireflux surgery is an alternative to long-term medical management of GERD. A 7-year trial comparing antireflux surgery to continued PPI use found both strategies to be similarly effective in controlling symptoms in patients with erosive esophagitis [38]. Surgery may be a reasonable option for patients who choose not to take medications, especially if there is good documentation of abnormal esophageal acid exposure, good symptom control on PPI, and documented symptom association with reflux events during pH testing. Surgery is particularly suited for those patients in whom troublesome regurgitation cannot be controlled with medication [6]. Surgical results in patients

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**Figure.** Treatment algorithm for reflux disorders. EGD = esophagastroduodenoscopy. (Adapted from reference 42.)
with “refractory heartburn” or atypical symptoms thought to be related to reflux are not as good as those seen in patients who respond to medical therapy [10]. Therefore, before embarking on antireflux surgery in patients who “fail” medical therapy, a thorough evaluation to include endoscopy, esophageal manometry, and pH monitoring is important to confirm that reflux is present and the likely etiology of persistent complaints and to exclude other causes of symptoms. Since there is no evidence that antireflux surgery prevents development or progression of Barrett’s esophagus in patients with GERD, surgery solely for this indication is inappropriate [6].

**SUMMARY**

GERD is frequently encountered in the primary care setting. In fact, the management of GERD has shifted away from gastroenterologists to primary care physicians for the vast majority of patients. Since patients with symptoms that are not adequately controlled often have associated reduction in quality of life which results in significant direct and indirect societal costs, it is important that primary care providers recognize how to expeditiously diagnose and effectively manage GERD sufferers.

Pragmatically, GERD has evolved into a symptom-based condition in which heartburn and regurgitation form the basis of diagnosis. Symptom response to antisecretory therapy (primarily PPIs) not only confirms the diagnosis but is the accepted goal of treatment. In most cases, patients with typical GERD symptoms will respond to 8 to 12 weeks of PPI treatment without the need for additional diagnostic testing. At that time, the dose of medication should be reduced to the lowest level and interval needed to maintain control of symptoms. This may reduce the likelihood of adverse events, although for the majority individuals even chronic PPI use is safe and well tolerated. Those patients who do not have an adequate response to once daily PPI therapy should be queried specifically on proper meal-associated dosing and adherence with treatment. In compliant patients failing once daily treatment, a trial of twice-daily PPI or longer acting PPI therapy is appropriate before considering symptoms to be refractory.

As important as recognizing GERD is recognizing what is not GERD. Always consider non–GERD-related symptoms in patients not responding to PPIs and exclude a cardiac etiology of complaints when appropriate. Specialist referral is the correct approach for those patients with PPI “refractory” symptoms or with risk factors for complications such as Barrett’s esophagus since further diagnostic testing is likely required.

Patients referred to the gastroenterologist with persistent symptoms on twice daily PPI therapy represent a particular diagnostic and therapeutic dilemma. In most cases, their symptoms are not due to inadequate acid suppression. More commonly their symptoms are due to a non-acid etiology. In these patients, upper endoscopy, ambulatory pH monitoring, and esophageal motility studies may shed light on the diagnosis and guide further therapy. It is especially important that primary care providers and specialists communicate and work together managing those patients with persistent symptoms despite adequate medical therapy. This will avoid unnecessary diagnostic tests, continuation of ineffective medication, and ill-advised surgery.

Corresponding author: Brian Behm, MD, MS, Univ. of Virginia Health System, Box 800708, Charlottesville, VA 22908, bwb2c@virginia.edu.

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