



Refractory Gastroesophageal Reflux Disease and Functional Heartburn

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KEYWORDS

- Gastroesophageal reflux disease • Reflux hypersensitivity • Functional heartburn
- Fundoplication • Proton pump inhibitor • Magnetic sphincter augmentation

KEY POINTS

- Heartburn can be considered PPI refractory when it does not respond to double-dose PPI therapy (first dose taken 30–60 minutes before breakfast, second dose taken 30–60 minutes before dinner).
- PPIs can eliminate all endoscopic and histologic evidence of eosinophilic esophagitis, and therefore PPIs should be stopped for 3 to 4 weeks if possible before performing diagnostic endoscopy for patients with PPI-refractory heartburn.
- Reflux hypersensitivity is diagnosed when systematic workup reveals no esophageal endoscopic, histologic, or motility abnormalities to account for heartburn, and esophageal MII-pH monitoring reveals normal esophageal acid exposure with a positive symptom index (SI) or positive symptom association probability (SAP) for heartburn.
- Functional heartburn is diagnosed when systematic workup reveals no esophageal endoscopic, histologic, or motility abnormalities to account for heartburn, and esophageal MII-pH monitoring reveals normal esophageal acid exposure with a negative SI or negative SAP for heartburn.

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PROBLEMS WITH DEFINING “REFRACTORY GASTROESOPHAGEAL REFLUX DISEASE”

There is no clear consensus regarding the precise definition of the term refractory GERD. GERD can be complicated by reflux esophagitis and peptic esophageal strictures, which occasionally can be difficult to treat and hence might be considered refractory. Patients with GERD typically complain of heartburn and regurgitation, symptoms that usually respond well to treatment but sometimes do not, and GERD can have many notoriously difficult-to-treat atypical symptoms, such as chest pain, chronic cough, hoarseness, and throat clearing.¹ Furthermore, there are many

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different types of treatments for GERD, including lifestyle modifications, antacids, alginates, acid-reducing medications, such as proton pump inhibitors (PPIs) and histamine H₂ receptor antagonists (H₂RAs), antireflux medications, such as baclofen, endoscopic procedures, such as transoral incisionless fundoplication (TIF), and surgical procedures, such as fundoplication. Although the term refractory GERD conceivably could be applied to any one or combination of the above problems that do not respond to any number of procedures or medications given for different durations in variable dosages, the term usually is used for symptoms that are assumed to be due to GERD and that have not responded to a trial of PPI therapy.

The PPIs are the most effective available medical treatment for GERD, and the US Food and Drug Administration (FDA) approves once-daily PPI dosing for patients with GERD. The FDA does not approve double-dose PPI therapy and, for patients whose symptoms are refractory to the conventional PPI dosage, doubling the dose usually achieves only modest additional therapeutic benefit.² Nevertheless, patients with GERD generally are not considered “PPI-refractory” until they have been on a double dose of PPIs with the first dose taken 30 to 60 minutes before breakfast and the second dose taken 30 to 60 minutes before dinner. Sifrim and Zerbib have proposed that patients with troublesome heartburn and regurgitation who do not respond to 12 weeks of double-dose PPIs can be considered to have PPI-refractory reflux symptoms.³ Alternatively, Yadlapati and Delay have defined “PPI-refractory GERD” as persistent troublesome GERD symptoms with objective evidence of GERD after 8 weeks of double-dose PPI therapy.⁴ These definitions, which might be useful as criteria for clinical studies, might be too restrictive for rigorous application in clinical practice.

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PPIs can heal reflux esophagitis in the large majority of cases,⁵ but they are considerably less effective for eliminating GERD symptoms, which allegedly persist in up to 40% of patients who take PPIs for GERD.³ Indeed, PPI-refractory GERD is the most common reason for GERD-related referrals to gastroenterologists.⁶ However, a careful medical history often will reveal that what patients perceive as persistent “GERD symptoms” during PPI treatment either are not GERD symptoms at all (eg, bloating, early satiation) or are symptoms that can have multiple causes other than GERD (eg, cough, hoarseness, throat clearing), and hence might not be due to GERD. Although heartburn and regurgitation, the cardinal symptoms of GERD, are far more likely to respond to PPIs than the atypical symptoms, a PPI response is neither a sensitive nor specific test for GERD.⁷ In 1 study in which 299 primary care patients with heartburn, regurgitation, or chest pain were treated empirically with esomeprazole 40 mg every day for 2 weeks, only 67% of those with objective evidence of GERD (by endoscopy or esophageal pH monitoring) experienced a symptomatic response to this “PPI test,” whereas 60% of those with no objective evidence of GERD nevertheless had a positive PPI test (ie, a symptomatic response to PPIs).⁸

Among the atypical GERD symptoms, noncardiac chest pain seems to have the best response to PPIs, especially for patients who also have objective evidence of abnormal acid reflux.¹ A systematic review of randomized controlled trials of PPIs for chest pain found that they were beneficial in 56% to 85% of patients with chest pain who had objective evidence of GERD by pH monitoring or endoscopy, but in only 0% to 17% of patients without such objective evidence.⁹ The efficacy of PPIs for atypical, extraesophageal GERD symptoms, such as throat clearing, hoarseness, and chronic cough is much less clear and much more controversial. Some observational studies have documented PPI efficacy in relieving these symptoms, but controlled trials have not consistently demonstrated a benefit of PPIs over placebo for patients with such “extraesophageal GERD.”^{10–14} Furthermore, although

physicians often assume (often with little or no evidence) that GERD is the cause of these extraesophageal symptoms, that assumption is incorrect in many, if not most cases.¹⁵

Laryngopharyngeal reflux (LPR) disease is an especially contentious condition for which there is no diagnostic “gold standard,” and no reliably effective treatment.¹⁶ Even the laryngoscopic demonstration of LPR is weak evidence that GERD is the underlying condition. In 1 study of 52 healthy volunteers (with no history of GERD or ear, nose, and throat problems) who had flexible videolaryngologic examinations reviewed by experts, at least 1 sign of LPR was detected in 93% of those healthy study subjects.¹⁷ Thus, when managing patients with atypical, extraesophageal symptoms, clinicians should be cautious about making a diagnosis of refractory LPR disease, especially if there is only weak evidence that GERD is the underlying cause. Use of the terms refractory GERD or “refractory LPR” in such cases can bias clinical decision making, because the underlying assumption for the use of both terms is that GERD is the cause of the problems, and this can result in inappropriate use of invasive GERD treatments for patients whose symptoms are not due to GERD. A detailed discussion of the diagnosis and management of LPR disease is beyond the scope of this article and is covered extensively in Caroline M. Barrett and colleagues’ article, “[Laryngopharyngeal Reflux and Atypical Gastroesophageal Reflux Disease](#),” in this issue. The reader is also referred to an excellent recent review of this topic.¹⁶ The remainder of this report will deal with the management of patients who have the typical GERD symptoms of heartburn and regurgitation that are refractory to PPI therapy.

PROTON PUMP INHIBITOR PHARMACODYNAMICS AND PREPARATIONS

Because PPIs are vulnerable to degradation by gastric acid, most are manufactured with an acid-resistant enteric coating that delays their release and absorption. Also, all of the PPIs are prodrugs that must be converted into an active, sulfenamide form by the acid produced by the proton pumps (H^+ , K^+ -ATPases) of gastric parietal cells. This sulfenamide form disables those proton pumps by binding to them covalently.

a Because PPIs can bind only to proton pumps that are actively secreting acid, PPIs should be dosed before meals to provide maximal acid suppression. In the fasting state, fewer than 10% of gastric proton pumps are active, whereas approximately 70% are active when stimulated by meals.¹⁸ Thus, PPIs should be taken 30 to 60 minutes before meals, the optimal time to enable their absorption and transport to actively secreting parietal cells. One study of 100 patients with persistent GERD symptoms on PPI therapy found that 54 took the medication incorrectly (21 >60 minutes before meals, 16 after meals, 15 at bedtime, 2 as needed).¹⁹ Thus, it is important to ask patients with PPI-refractory GERD how they are taking their PPIs, and to stress the importance of taking them 30 to 60 minutes before meals. A recent study reported in abstract form found that approximately 11.5% of patients referred to Veterans Affairs GI clinics for PPI-refractory heartburn responded to this simple clinical maneuver.^{20,21}

b Although all available PPIs are effective for healing reflux esophagitis when given in their standard dosages, the acid suppression potency of the different PPI preparations varies widely. If relative acid suppression potencies of individual PPIs (based on their effects on mean 24-hour intragastric pH) are standardized to omeprazole in terms of “omeprazole equivalents” ([OEs], with omeprazole having an OE of 1.00), the relative potencies of standard-dose pantoprazole, lansoprazole, omeprazole, esomeprazole, and rabeprazole have been estimated at 0.23, 0.90, 1.00, 1.60, and 1.82 OEs, respectively.^{22,23} Thus, 4 pantoprazole tablets are needed to achieve the acid-suppressing capability of 1 omeprazole tablet. Individual patients also can exhibit considerable

variability in their response to different PPIs.²⁴ These data suggest that it might be useful to switch patients with PPI-refractory symptoms from one PPI to another, preferably more potent one, although there are few clinical data that support the clinical efficacy of this maneuver.

PROTON PUMP INHIBITOR-REFRACTORY HEARTBURN

Heartburn, the most typical and most frequent symptom of GERD, can be defined as a burning sensation in the retrosternal area.²⁵ Patients frequently relate that the burning sensation moves up the chest and that it is relieved by antacids. When describing heartburn, patients typically wave an open hand over the sternum, unlike patients with angina pectoris who might hold a clenched fist over the left chest when describing their pain (Levine sign). The physician's first step in the evaluation of a patient with PPI-refractory heartburn is to ask the patient for a detailed description of the symptom. A patient's concept of what the term "heartburn" means can differ dramatically from the physician's concept and, when asked for a description, many patients who say or were told that they have heartburn will describe a symptom that cannot originate from the esophagus.²⁶ However, even if the description is consistent with the heartburn of GERD, heartburn is by no means specific for GERD. Patients with eosinophilic esophagitis (EoE) or esophageal motility disorders, such as achalasia can experience heartburn, and balloon distention of the esophagus can elicit retrosternal burning typical of heartburn.²⁷

Five major mechanisms might explain heartburn that does not respond to PPIs²⁸: (1) the PPIs have not normalized esophageal acid exposure; (2) the PPIs have normalized esophageal acid exposure but there is reflux hypersensitivity, the condition in which persistent "physiologic" reflux events (acidic or nonacidic) evoke heartburn²⁹; (3) the sensation of heartburn is caused by an esophageal disorder other than GERD, such as EoE or achalasia; (4) the sensation of heartburn is caused by an extraesophageal disorder, such as heart or gallbladder disease; or (5) there is functional heartburn, meaning that the sensation of heartburn is not caused by GERD, reflux events, or any other identifiable histopathologic, motility, or structural abnormality.²⁹ A rigorous, systematic evaluation that includes careful medical history, endoscopy with esophageal biopsy, esophageal manometry, and esophageal multichannel intraluminal impedance (MII)-pH monitoring can distinguish among these mechanisms as discussed below.

Proton Pump Inhibitors Have Not Normalized Esophageal Acid Exposure

Patients who have a severe reflux diathesis, such as those with long-segment Barrett's esophagus, often have persistently abnormal acid reflux despite high-dose PPI therapy. In 1 study of 31 patients with long-segment Barrett's esophagus treated with esomeprazole 40 mg twice a day, 24-hour esophageal pH monitoring demonstrated persistently abnormal acid reflux in 23%.³⁰ However, PPI-refractory heartburn is unusual in Barrett's patients, even when abnormal acid reflux persists during PPI therapy.³¹ In other words, PPIs usually eliminate heartburn in patients with Barrett's esophagus even when they do not normalize esophageal acid exposure.

Approximately one-third of patients with PPI-refractory GERD symptoms who are treated with PPIs in standard, once-daily dosage will have persistently abnormal acid reflux exposure found on esophageal pH monitoring studies.^{32,33} However, abnormal acid reflux is decidedly unusual in patients who take PPIs twice-daily. In 1 study of patients with PPI-refractory GERD symptoms on twice-daily PPIs, abnormal esophageal acid exposure was found in only 7% of 52 patients with typical GERD

symptoms, and in only 1 % of patients with extraesophageal GERD symptoms.³² Thus, persistently abnormal acid reflux is an uncommon cause of PPI-refractory heartburn.

Proton Pump Inhibitors Have Normalized Esophageal Acid Exposure, but There Is Reflux Hypersensitivity

By convention, esophageal pH monitoring identifies acid reflux when esophageal pH values fall below 4. In contrast, esophageal impedance monitoring detects the reflux of all gastric material whether it is acidic (pH <4), weakly acidic (pH >4 to <7), or alkaline (pH >7). In the era before esophageal impedance monitoring was available, the term “acid hypersensitivity” was used to describe patients who had normal esophageal acid exposure by esophageal pH monitoring, but in whom “physiologic” episodes of acid reflux were associated with heartburn. More recent esophageal MII-pH monitoring studies have established that reflux episodes with pH >4 also can be associated with heartburn. Consequently, the term acid hypersensitivity has been replaced by the term “reflux hypersensitivity,” the condition in which patients with normal esophageal acid exposure have reflux episodes (acidic, weakly acidic, or alkaline) associated with heartburn.²⁹ It has been estimated that 28% to 36% of patients who do not respond to twice-daily PPI therapy have reflux hypersensitivity.¹

The mechanisms through which reflux episodes cause heartburn are poorly understood. It has been proposed that refluxed acid (pH <4) causes heartburn by activating acid-sensitive nociceptors in the esophageal epithelium.³¹ The mechanism whereby the reflux of less acidic material causes heartburn is even less clear. Perhaps weakly acidic refluxate (pH >4 and <7) can trigger the same nociceptors activated by more strongly acidic material. Alternatively, the reflux of irritants other than acid (eg, bile salts) might trigger the nociceptors that convey heartburn, or large-volume reflux might cause esophageal distention that activates those nociceptors. It also has been proposed that reflux can result in sustained contractions of esophageal longitudinal muscle that elicit the sensations of heartburn and chest pain.^{34,35}

The diagnosis of reflux hypersensitivity requires the demonstration of an association between reflux episodes and symptom episodes in patients who have normal esophageal acid exposure.²⁹ Esophageal pH or MII-pH monitoring studies typically use 2 indices to identify a significant association between reflux and symptom episodes: the symptom index (SI) and the symptom association probability (SAP). To calculate the SI, the total number of reflux episodes that are associated with symptom episodes is divided by the total number of symptom episodes recorded during the monitoring period.³⁶ If $\geq 50\%$ of all symptom episodes are associated with an episode of reflux, then the SI is considered positive. The validity of the SI has been questioned for several reasons, but primarily because it does not consider the total number of reflux events. For example, if a patient has 100 episodes of acid reflux during the monitoring period but only 1 symptom episode, and that symptom episode by chance happens to correspond with one of the 100 acid reflux episodes, then that patient would have an SI of 100%, spuriously suggesting a very strong association between symptoms and reflux episodes.

The SAP was developed in an attempt to circumvent the shortcomings of the SI.³⁷ To determine the SAP, the 24-hour monitoring period is divided into 720 two-minute increments, and each increment is evaluated for the occurrence of reflux and symptom episodes. Then, a Fisher exact test is performed to determine a *P* value for the probability that the reflux and symptom events are randomly distributed. The SAP is determined by subtracting the calculated *P* value from 1, and the remainder is multiplied by 100%. A positive SAP is defined as greater than 95%, meaning that the chance that reflux and symptom events are randomly

distributed throughout the monitoring period has a *P* value of less than 0.05. In other words, a positive SAP identifies a significant association between reflux and symptom episodes. Unfortunately for clinical purposes, SAP and SI results do not always agree and, despite the theoretic advantages of the SAP, its clinical superiority over the SI has not been established unequivocally. In addition, the validity of the SAP for distinguishing reflux hypersensitivity from functional heartburn has been questioned.^{38,39}

Heartburn Is Caused by an Esophageal Disorder Other than Gastroesophageal Reflux Disease

Esophageal inflammation of any cause conceivably might induce the retrosternal burning discomfort of heartburn, but EoE is the inflammatory disorder most likely to be confused with GERD. Patients with EoE commonly have a history of atopy, are younger than the typical patient with GERD, and usually present because of dysphagia and food impaction rather than heartburn. Nevertheless, confusion with GERD can arise, especially for patients whose major complaint is heartburn.⁴⁰ The characteristic endoscopic findings of EoE are esophageal exudates, rings, edema, furrows, and strictures, and the diagnosis is established when esophageal biopsies show greater than 15 eosinophils per high power field and other causes of esophageal eosinophilia are excluded. The esophagus can appear endoscopically normal in approximately 10% of patients with EoE, so esophageal biopsies should be taken routinely in any patient having endoscopy for PPI-responsive heartburn irrespective of the endoscopic appearance of the esophagus.

Until recently, PPIs were used as a test to distinguish GERD from EoE with the assumption that only the acid-peptic disease (GERD) could respond to PPI therapy.⁴¹ For patients with PPI-refractory heartburn, therefore, it was not common practice to stop PPIs before diagnostic endoscopy to look for EoE since PPI responsiveness was thought to exclude that diagnosis. More recent data have shown that EoE can respond to PPIs, and PPIs are now considered a treatment for EoE, not a diagnostic test for the condition.⁴² Because it is now well established that PPIs can eliminate the endoscopic and histologic signs of EoE, it follows that an endoscopy performed for a patient on PPIs cannot rule out EoE. When EoE is a diagnostic consideration, as it is for patients with PPI-refractory heartburn, then PPIs should be discontinued for 3 to 4 weeks before diagnostic endoscopy whenever possible.⁴³ Stopping PPIs will also be helpful for determining the severity of GERD, since PPIs can also eliminate the endoscopic signs of reflux esophagitis. Indeed, it is not appropriate to make a diagnosis of nonerosive reflux disease (NERD) based on an endoscopy performed for patients taking PPIs. Patients with achalasia, an esophageal motility disorder that typically causes dysphagia, frequently complain of heartburn that can be confused with GERD.⁴⁴ In achalasia, loss of neurons in the wall of the esophagus results in inadequate lower esophageal sphincter (LES) relaxation with swallowing, and abnormal function in muscles of the esophageal body. It is not clear whether the sensation of heartburn in achalasia is caused by the abnormal esophageal motor activity, or by acid that might reflux into the esophagus when the LES finally does relax. Abnormal esophageal acid exposure has been documented in patients with achalasia, although it is not clear whether the acid in the esophagus is hydrochloric acid refluxed from the stomach, or lactic acid produced by the fermentation of carbohydrate retained in the achalasic esophagus.⁴⁵ Patients with achalasia can have PPI-refractory heartburn, a feature that occasionally has resulted in achalasia patients having Nissen fundoplications to treat heartburn mistakenly attributed to GERD. Nissen fundoplication can cause debilitating dysphagia in this setting.⁴⁶ Therefore, for patients considering

fundoplication for the treatment of GERD, preoperative esophageal manometry is recommended to avoid this potentially devastating mistake.

Heartburn Is Caused by an Extraesophageal Disorder

Because both GERD and coronary artery diseases (CADs) are associated with obesity,⁴⁷ it is not surprising that obese patients with CAD frequently have GERD.⁴⁸ Angina can be described as burning in character and it is certainly conceivable that angina might be incorrectly diagnosed as heartburn due to GERD.⁴⁹ However, there is surprisingly little published documentation of this error. Patients can misunderstand what is meant by the term heartburn, and might mistakenly use that term for what are in fact typical anginal symptoms.²⁶ If such patients tell their physicians that they have heartburn, and the physicians take that history at face value without asking for a description of the heartburn, then angina due to CAD might well be confused with GERD. It is not clear how often angina causes retrosternal burning discomfort that could not be distinguished from the heartburn of GERD by a careful history. Nevertheless, since the consequences of misdiagnosing CAD as GERD can be catastrophic, clinicians should consider the possibility that CAD might cause a heartburn sensation that does not respond to PPIs, especially in older patients with other risk factors for CAD.

The pain of pancreatic or biliary tract disease does not respond to PPIs, and conceivably could be confused with heartburn if it is burning in character and referred to the epigastrium or lower chest. As is the case for angina due to CAD, however, it is not clear how often pancreaticobiliary disease causes retrosternal burning discomfort that a careful history could not distinguish from the heartburn of GERD. Nevertheless, clinicians should consider the possibility that pancreaticobiliary diseases might underlie PPI-refractory pain, especially in patients with other risk factors for those diseases.

FUNCTIONAL HEARTBURN

When the above mechanisms have been excluded, PPI-refractory heartburn can be considered functional.²⁹ Unfortunately, “functional” is a nonspecific and potentially stigmatizing term that has engendered considerable confusion and contention among experts over the years. In 1992, a group of such experts met in Rome to formulate a classification system for functional gastrointestinal disorders, and so devised the “Rome criteria” to codify gastrointestinal syndromes that were not from any named histopathologic, motility, or structural abnormality. Since then, there have been 3 more iterations of the Rome criteria, all struggling with use of the term functional. It has become clear that some patients with so-called functional disorders can have subtle histopathologic and physiologic abnormalities that have no specific names. Rome IV, the most recent iteration of the Rome criteria, discourages use of the term functional, and suggest that the traditional functional gastrointestinal disorders should instead be called “disorders of gut-brain interaction.”⁵⁰ Nevertheless, Rome IV retains the term “functional heartburn” and, adding to the confusion, also deems reflux hypersensitivity to be a “functional gastrointestinal disorder.”²⁹

Rome IV defines functional heartburn as retrosternal burning discomfort or pain that is, refractory to “optimal antisecretory therapy” in the absence of GERD, histopathologic mucosal abnormalities, major motor disorders, or structural explanations.²⁹ Functional heartburn is distinguished from reflux hypersensitivity by esophageal pH or MII-pH monitoring studies that show no association between reflux episodes and heartburn episodes (ie, SI <50% and/or SAP ≤95%). It has been estimated that 29% to 39% of patients who do not respond to twice-daily PPI therapy have functional

heartburn.¹ The mechanisms underlying functional heartburn are not known, but they seem to be unrelated to gastroesophageal reflux. Consequently, medications and procedures aimed at controlling reflux should not be prescribed for patients with functional heartburn, and treatment can focus on the use of neuromodulators or cognitive behavior therapy (see later discussion). Although Rome IV considers reflux hypersensitivity to be a functional disorder, a recent randomized trial of medical and surgical therapy for patients with PPI-refractory heartburn (so far reported only in abstract form) found that fundoplication was superior to medical treatment for highly selected patients with reflux hypersensitivity.²⁰

REGURGITATION

- a PPIs inhibit gastric acid secretion but do nothing to correct the reflux diathesis underlying GERD.⁵¹ Consequently, it is not surprising that PPIs have limited efficacy in relieving the typical GERD symptom of regurgitation. Experts at the Montreal consensus conference on GERD in 2006 defined regurgitation as “the perception of flow of refluxed gastric content into the mouth or hypopharynx.”²⁵ However, the Reflux Disease Questionnaire (RDQ), a validated instrument used in the evaluation of patients with GERD, has describes 2 symptoms that can be considered regurgitation (1) an acid taste in the mouth and (2) unpleasant movement of material upward from the stomach. Studies that have used the RDQ found that regurgitation is a troublesome symptom in approximately 50% of patients with GERD, and that PPIs relieve regurgitation only marginally better than placebo.^{14,52} For patients with PPI-refractory regurgitation as a predominant symptom, further medical therapy is notoriously ineffective and antireflux procedures are far better at relieving the symptom (see later discussion).
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TREATMENTS OTHER THAN PROTON PUMP INHIBITORS FOR PROTON PUMP INHIBITOR-REFRACTORY HEARTBURN THAT IS REFLUX RELATED

Antireflux Lifestyle Modifications

Antireflux lifestyle modifications (elevation of the head of the bed on 4" to 6" blocks, weight loss for overweight patients, avoiding recumbency for several hours after meals, avoiding bedtime snacks, and avoiding fatty foods, smoking and alcoholic beverages) were once considered first-line therapy for GERD, but their usefulness has dwindled since the introduction of PPIs into clinical practice in 1989. Only very limited data support the efficacy of these lifestyle modifications in controlling GERD symptoms at all, and data on their efficacy in patients with PPI-refractory GERD are virtually nonexistent. Nevertheless, it seems reasonable to try these modifications for patients with PPI-refractory GERD, especially those with reflux hypersensitivity or troublesome regurgitation who might benefit from modifications that reduce reflux episodes.

Baclofen

Transient LES relaxation (TLESR) is a major mechanism underlying episodes of gastroesophageal reflux in patients with GERD as well as in normal individuals.⁵³ Unlike the brief, appropriate LES relaxations induced by swallowing, TLESRs are not preceded by swallowing and last more than 10 seconds. TLESRs are part of the normal belch reflex triggered by gaseous distention of the stomach, enabling the gas trapped in the stomach to be expelled in the form of a belch. TLESRs are mediated by the nucleus tractus solitarius in the medulla, which integrates sensory information from the stomach and directs the neural circuits that produce TLESRs. Neurons with γ -aminobutyric acid B (GABA_B) receptors inhibit TLESRs, and the GABA_B agonist baclofen can decrease their frequency.⁵⁴ Unfortunately, baclofen often causes intolerable

drowsiness and other side effects, and studies on its efficacy for PPI-refractory GERD are very limited. The development of other GABA_B agonists, including arbaclofen placarbil and lesogaberan was abandoned because of poor clinical efficacy.^{55,56}

Alginates

b When alginates come into contact with gastric acid, they precipitate into a gel that forms a “raft” that floats on top of the gastric contents. This raft poses a mechanical barrier that displaces the postprandial acid pocket (a layer of strong, unbuffered gastric acid that forms at the gastroesophageal junction after meals) distally into the stomach and out of the esophagus. Alginates seem to be more effective than placebo and antacids for treating GERD symptoms,⁵⁷ and limited data suggest that adding alginates to PPI therapy might provide better control of GERD symptoms than PPIs alone in patients with NERD.⁵⁸

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Adding an H₂ Receptor Antagonist at Bedtime to Proton Pump Inhibitor Therapy

Studies using gastric pH monitoring have shown that some 70% to 80% of individuals treated with twice-daily PPIs experience nocturnal gastric acid breakthrough, defined as a fall in gastric pH below 4 for more than 1 hour at night.⁵⁹ Nocturnal gastric acid breakthrough provides the opportunity for acid reflux during sleep in patients with GERD who take PPIs. Nocturnal gastric acid breakthrough seems to be largely a histamine-driven event, and short-term studies have shown that nocturnal gastric pH can be maintained above 4 by adding a bedtime dose of an H₂RA.⁶⁰ However, the clinical importance of nocturnal gastric acid breakthrough is not clear, and tachyphylaxis to the antisecretory effect of H₂RAs develops quickly.⁶¹ Presently, few data support the clinical efficacy of adding an H₂RA at bedtime for patients with persistent GERD symptoms on PPI therapy.⁶²

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Potassium-Competitive Acid Blockers

Like PPIs, the potassium-competitive acid blockers (P-CABs) block gastric acid production by inhibiting the H⁺, K⁺-ATPase of the gastric parietal cell. Unlike PPIs, the P-CABs are not degraded by gastric acid and so require no enteric coating that would delay their absorption, and P-CABs are active drugs, not prodrugs. Also unlike PPIs, the P-CABs bind ionically (not covalently) to proton pumps, and since they will bind both active and inactive proton pumps they do not have to be dosed around meals. Thus, P-CABs can block gastric acid secretion more quickly than PPIs, and perhaps even more effectively than PPIs.⁶³ However, P-CABs are not presently available for widespread clinical use outside of Japan. Japanese studies on the P-CAB vonoprazan have demonstrated its efficacy in healing erosive esophagitis not healed by conventional-dose PPIs.⁶⁴ However, despite their theoretic advantages over PPIs, it is not clear that P-CABs are any more effective than PPIs for treating GERD in Western patients. If P-CABs become available for use in Western countries, it is anticipated that they might be especially useful for patients with persistently abnormal esophageal acid exposure on double-dose PPI therapy.

Neuromodulators

Neuromodulators, such as tricyclic antidepressants, trazadone, and selective serotonin reuptake inhibitors are thought to dull visceral hypersensitivity through effects on central nervous system pain-processing pathways. For patients with reflux hypersensitivity and functional heartburn, neuromodulators used in dosages that allegedly do not alter mood seem to have some efficacy in relieving heartburn.^{65–67} However, 1 randomized controlled trial found that imipramine did not relieve symptoms any more

effectively than placebo in these patients, although there were benefits of imipramine for improving quality of life.⁶⁸ Unfortunately, the neuromodulators often have intolerable and sometimes dangerous side effects, and studies on their efficacy for PPI-refractory heartburn are few and of short duration.

Cognitive Behavioral Therapy

Limited data suggest that cognitive behavioral therapy can be an effective treatment for patients with functional heartburn and reflux hypersensitivity.⁶⁹ A health psychologist with specialization in gastroenterology can be a valuable asset in patient management but, unfortunately, the availability of such therapists is limited.

Antireflux Procedures

Unlike PPIs, which target gastric acid but do nothing to correct the underlying reflux diathesis, antireflux procedures (surgical and endoscopic) are designed to create a barrier to the reflux of all gastric contents. Among all the antireflux procedures, fundoplication is considered the gold standard for its efficacy in improving the physiologic parameters of GERD, such as LES pressure and esophageal acid exposure time.⁷⁰ In principle, fundoplication should be an effective treatment for any PPI-refractory GERD symptom that is reflux related. In practice, however, patients with "GERD symptoms" that do not respond to PPIs often do not respond to surgery either.⁷¹ When surgery fails to relieve PPI-refractory GERD symptoms, the failure is often one of poor patient choice rather than failure of the operation to control reflux. Functional disorders are a more common cause of PPI-refractory heartburn than persistent GERD, and surgery is unlikely to benefit a patient with functional complaints.^{20,21} When considering surgery for patients with PPI-refractory heartburn, a thorough preoperative workup is required to exclude the functional and non-GERD organic disorders that might cause the symptom, and to ensure that the heartburn is indeed reflux related.

Laparoscopic fundoplication is an effective and reasonably safe procedure for carefully selected patients with PPI-refractory heartburn that is reflux related. Modern laparoscopic antireflux surgery has a short-term complication rate (infection, bleeding, esophageal perforation) of approximately 4%, a very low surgical mortality rate, and a GERD recurrence rate of approximately 18% within 5 years postoperatively.⁷² Fundoplication can be complicated by dysphagia and by an inability to belch and vomit, and occasionally by other troublesome symptoms.

Magnetic sphincter augmentation (MSA) was developed as a less invasive and more readily reversible GERD treatment than fundoplication. In MSA, the surgeon fastens a bracelet of magnetic beads (the LINX Reflux Management System) around the distal esophagus to bolster the LES and prevent reflux. MSA seems to be an effective and durable therapy in carefully selected patients with GERD with symptoms incompletely controlled by PPIs, usually those with small hiatal hernias (<3 cm), mild or no reflux esophagitis, and documented abnormal esophageal acid exposure.⁷³ For patients in whom regurgitation is the predominant PPI-refractory symptom, a recent randomized trial has established the unequivocal superiority of MSA over twice-daily PPIs.⁷⁴

Many endoscopic therapies for GERD have been developed, and most of the devices have been removed from the marketplace because of concerns regarding safety and efficacy. Presently, the only endoscopic GERD treatments still widely available are radiofrequency antireflux treatment (Stretta) and TIF. The role of Stretta is particularly controversial. Some data suggest that Stretta can be effective in carefully selected patients with GERD who are dissatisfied with PPI therapy.⁷⁵ However, a recent

systematic review and meta-analysis concluded that Stretta does not significantly alter physiologic parameters, such as esophageal acid exposure and LES pressure, does not reliably enable patients to stop PPIs, and does not significantly improve health-related quality of life.⁷⁶ Randomized trials have shown that TIF is effective for treating troublesome regurgitation, at least in the short term.^{77,78} Unfortunately, TIF seems to break down over time, and its long-term benefit in controlling GERD is not established and highly questionable.⁷⁰

A system for GERD treatment via electrical stimulation of the LES is being studied. This system uses a pacemaker-like generator (EndoStim) that is implanted in the abdominal wall and connected through a cable to a pair of electrodes that are sutured to the LES muscle. Preliminary data have shown some short-term efficacy for this technique, but complications, including bowel injury during implantation and erosion of the electrode leads have been reported.⁷⁹ The device presently is not widely available, and it is not yet clear precisely how it works to control GERD. Further studies are needed before it can be recommended for clinical use.

MANAGEMENT OF PATIENTS WITH HEARTBURN REFRACTORY TO PROTON PUMP INHIBITOR THERAPY

Fig. 1 outlines an approach to the management of patients with heartburn refractory to PPI therapy. The first step is to obtain a careful medical history to confirm that the patient truly has heartburn, and to identify warning symptoms, such as dysphagia, weight loss, and gastrointestinal bleeding that might require expedited evaluation. The history might also provide clues regarding the presence of extraesophageal disease (eg, heart, pancreaticobiliary) that might be causing the heartburn sensation, and that might require urgent evaluation.

Many patients referred to gastroenterologists for PPI-refractory heartburn already are taking PPIs in high dosage, but they often are taking the PPIs incorrectly. A trial of twice-daily PPI therapy should be implemented with explicit instruction to take the PPIs 30 to 60 minutes before breakfast and dinner. Consideration can also be given to switching PPIs, especially for patients already on twice-daily PPI treatment, and for those taking pantoprazole, which is the least potent of the available PPIs for gastric acid suppression. These steps can be taken before proceeding with invasive tests. If heartburn does not improve after 4 to 8 weeks of this PPI trial, further workup is required.

I recommend stopping PPIs if possible (some patients will not tolerate a period off PPIs) for 3 to 4 weeks before proceeding to endoscopic examination. Although the PPIs are stopped in anticipation of endoscopy, consideration can be given to performing esophageal pH monitoring. The utility of pH monitoring at this point in the workup is controversial.⁶⁵ The major argument for performing it here is that a normal esophageal pH monitoring study off PPIs eliminates GERD as a diagnostic concern, and thus should direct further diagnostic and therapeutic efforts at non-GERD disorders. The counterargument is that many patients will have an abnormal pH monitoring study off PPIs and, although this establishes the presence of GERD, it does not establish that GERD is the cause of the PPI-refractory heartburn and it does not explain why the patients have not responded to PPIs. The physician's assessment of the pretest probability for GERD can be used to guide the choice of whether or not to perform esophageal pH monitoring off PPIs. If the physician determines that there is a high pretest probability for GERD or that other tests already have established that the patient has GERD (eg, a previous endoscopy showed long-segment Barrett's esophagus or severe reflux esophagitis), then pH monitoring off PPIs is unlikely to provide useful

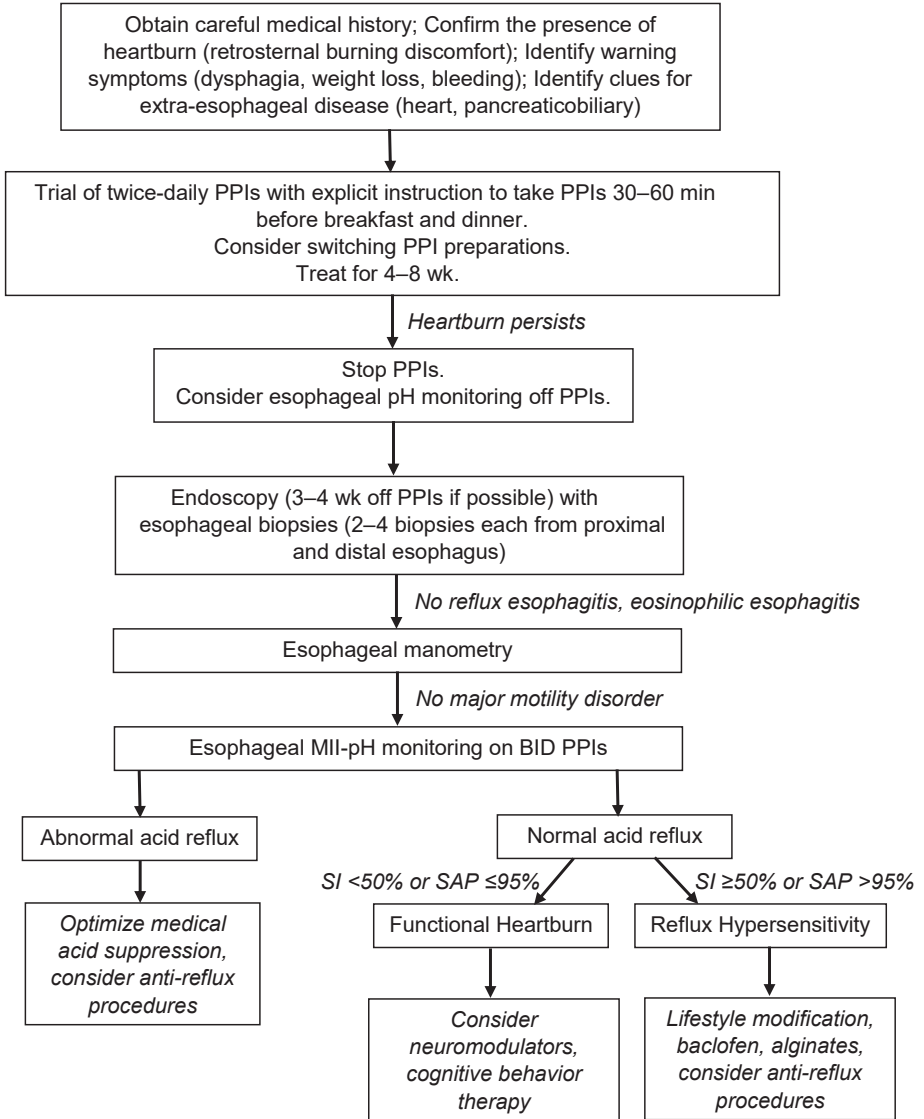


Fig. 1. Approach to the management of patients with heartburn refractory to PPI therapy.

information. Conversely, if the pretest probability for GERD is low (eg, the heartburn description is questionable or there has been no response whatsoever to PPIs), then esophageal pH monitoring can be helpful for guiding further evaluation and treatment.

It is important that PPIs be stopped for 3 to 4 if possible before performing diagnostic endoscopy. PPIs can eliminate the endoscopic and histologic signs of EoE, and so an endoscopy performed with a patient on PPI therapy cannot rule out EoE. PPIs also can eliminate all endoscopic signs of GERD, and so stopping PPIs might establish the presence of reflux esophagitis. Although it is common for physicians

to make a diagnosis of NERD when endoscopy for heartburn shows no reflux esophagitis, that diagnosis is inappropriate unless PPIs were stopped. Irrespective of the appearance of the esophagus, 2 to 4 biopsies should be taken from both the proximal and distal esophagus to look for EoE.

If endoscopy shows no evidence of EoE or reflux esophagitis, esophageal manometry is performed to identify motility abnormalities, such as achalasia or distal esophageal spasm that can cause the symptom of heartburn. If there is no major motility disorder, then esophageal MII-pH monitoring is performed with the patient on twice-daily PPIs. If there is persistent abnormal acid reflux, then therapy can be focused on optimizing medical acid suppression or on controlling reflux with an anti-reflux procedure. If there is normal acid reflux and the SI and/or SAP are negative (ie, SI <50%, SAP ≤95%), then the patient has functional heartburn, which might be treated with neuromodulators or with cognitive behavior therapy. If the SI and/or SAP are positive (ie, SI ≥50%, SAP >95%) in the patient with normal acid reflux, then reflux hypersensitivity is diagnosed. Patients with reflux hypersensitivity can be treated with antireflux lifestyle modifications, baclofen and alginates. Antireflux procedures, such as fundoplication and MSA can be recommended in highly selected patients.

DISCLOSURE

S.J. Spechler has served as a consultant for Takeda Pharmaceuticals, Frazier Life Sciences, Phathom Pharmaceuticals, and Ironwood Pharmaceuticals, and receives royalties as an author for UpToDate.

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