Treatment of Refractory Gastroesophageal Reflux Disease

Rishi D. Naik, MD, MSCI, Matthew H. Meyers, MD, and Michael F. Vaezi, PhD, MD, MS

Abstract: Gastroesophageal reflux disease (GERD) is a common disorder that is treated with lifestyle modification, weight loss, and medications, such as proton pump inhibitors (PPIs). An empiric course of PPI therapy is an effective and cost-effective strategy for the management of GERD. However, in some patients, PPI therapy and lifestyle changes are inadequate to control symptoms. When there is persistence of symptoms despite empiric therapy, patients are labeled as having refractory GERD. This label underestimates the wide differential diagnosis of foregut pathology that can mimic symptoms of GERD. A careful history of symptoms, response to PPI therapy, adherence, compliance, and timing helps elucidate if medication has been helping. When patients are refractory, alternative etiologies of GERD must be considered. Many of these alternatives can be determined on an upper endoscopy or with complementary testing, such as high-resolution esophageal manometry or gastric emptying testing as symptoms dictate. When an alternative cause is not found and index endoscopy is normal, additional testing with either traditional pH or impedance testing can be completed based on prior examination results and response to therapy. Further therapy, including medical, endoscopic, or surgical, can then be targeted at the etiology.

Gastroesophageal reflux disease (GERD) is a chronic condition related to the reflux of gastric contents into the esophagus that leads to troublesome symptoms (classically heartburn and regurgitation). GERD affects between 18% and 28% of North Americans, with studies suggesting that 20% to 40% of Americans have symptoms of GERD, making it the most prevalent gastrointestinal disorder in the United States. In addition to a significant compromise in quality of life, potential complications of GERD include strictures, dysphagia, esophagitis, Barrett esophagus, and esophageal adenocarcinoma.
Acid production plays a critical role in the development of heartburn. Proton pump inhibitors (PPIs) decrease acid production and are the mainstay of treatment for GERD. Despite the efficacy of PPI therapy, a significant percentage of patients with symptoms of GERD will not respond. It has been estimated that approximately 30% of patients with a presumed diagnosis of GERD will experience a lack of symptomatic improvement, either partially or fully, despite PPI therapy. The most common presentation of GERD at an outpatient gastroenterology office visit is unresolved symptoms following failure of PPI therapy.

Refractory symptoms of GERD are a challenging but important topic with potentially costly diagnosis, treatment, and management. However, it is necessary to delineate refractory symptoms of GERD (e.g., report of heartburn or regurgitation) that may not be GERD-related. This article focuses on recognizing refractory GERD and refractory symptoms of GERD, the differential diagnosis, and the role of diagnostic testing and therapeutic options.

**Definition**

GERD can be subdivided into erosive reflux disease or nonerosive reflux disease (NERD) based on endoscopic findings. Both types exhibit variable success with PPI therapy. Patients with NERD do not have findings of esophagitis on endoscopy but do have typical symptoms of GERD, with generally high esophageal acid exposure time on pH monitoring. In one study, patients with NERD, who make up to 70% of the GERD population, had a lower effective response rate to once-daily PPI therapy at 4 weeks compared to patients with erosive esophagitis (37% vs 56%, respectively), with a similar study showing comparable results. Patients who have a normal acid exposure time but a positive symptom index (SI) or symptom association probability (SAP) are classified as having reflux hypersensitivity. If heartburn remains the predominant symptom but the SI and SAP are normal, patients are classified as having functional heartburn according to the Rome IV criteria. Both of these functional esophageal disorders are the etiology of persistent symptoms in refractory GERD in up to 90% of patients. There is often concomitant typical GERD with these 2 functional esophageal disorders. According to one study, in 75% of patients with GERD refractory to once-daily PPI therapy, 62.5% had functional heartburn and 12.5% had reflux hypersensitivity. Given this predominance of functional esophageal disease overlap, treatments should be aimed at neuromodulation, psychological therapy, and complementary therapy as opposed to increased antireflux medications or surgical or endoscopic interventions.

Further complicating the definition of refractory GERD are the differential responses of the typical GERD symptoms to PPI therapy. Heartburn is more responsive than regurgitation to PPI treatment, and regurgitation is likely to play an important role in symptomatic GERD. Additionally, expert opinion varies on whether failing a standard dose of once-daily PPI therapy vs having a partial lack of response to twice-daily dosing should be considered as treatment failure. The American Gastroenterological Association recommended twice-daily PPI therapy for any patient with suspected GERD and an inadequate response to once-daily PPI therapy before assuming treatment failure. For the purposes of this article, refractory GERD will be defined as inadequate symptom response after at least 8 weeks of twice-daily PPI therapy. Once refractory GERD is suspected, the differential diagnosis of these symptoms should be explored.

**Differential Diagnosis for Refractory Gastroesophageal Reflux Disease**

Experts estimate that more than two-thirds of patients referred to a gastroenterologist with refractory GERD symptoms to PPI therapy do not have GERD. A study performed with pH-impedance monitoring showed that as much as 63% of refractory GERD patients report symptoms that cannot be correlated with GERD. The differential diagnosis for refractory GERD can be divided based on etiology (Table 1).

**Insufficient Acid Suppression or Increased Reflux**

Proton Pump Inhibitor Compliance and Timing Two observational studies have found that only 53.8% and 67.7% of patients, respectively, filled their PPI prescriptions at least 80% of the time. Timing of medication has also been shown to be a significant issue with PPI therapy. Optimal timing is 30 to 60 minutes before meals. One study revealed that only 46% of patients dosed PPIs at appropriate times. Another study reported that 36% of physicians do not give any directions or give inappropriate directions to patients regarding timing of their PPI therapy. In the United States, a study reported that 70% of primary care physicians and 20% of gastroenterologists encouraged patients to take their PPI at bedtime or believed timing to be unimportant. A cost-effective and first step for management includes a discussion on compliance of medication along with education on proper timing.

Cytochrome P450 2C19 Polymorphism PPIs are significantly metabolized by the liver enzyme cytochrome P450 2C19 (CYP2C19). Three possible genotypes exist for this enzyme: extensive metabolizers, intermediate
metabolizers, and poor metabolizers. Studies indicate that the PPI response rate varies between the 3 groups, with 52.2% of extensive metabolizers, 56.7% of intermediate metabolizers, and 61.3% of poor metabolizers responding effectively. Furthermore, patients who were extensive metabolizers were 66% more likely to experience refractory symptoms on standard-dose PPIs compared to poor metabolizers. The exact role of differential CYP2C19 activity remains unclear, as almost all studies have been performed with once-daily PPI therapy. However, in a study that examined PPI response rate comparing extensive to intermediate to poor metabolizers in both once-daily and twice-daily PPI therapy, the authors found that after 8 weeks of therapy for intermediate and extensive metabolizers, twice-daily PPI therapy was associated with a significantly higher sustained symptom response compared to once-daily therapy. There was no difference in the poor metabolizer group, suggesting that PPI metabolism may play a role in refractory GERD. Currently, there is insufficient evidence for genetic polymorphism testing for refractory GERD; an empiric PPI transition to CYP2C19-independent PPI therapy provides a more cost-effective strategy than performing genetic testing.

Weakly Acidic or Nonacid Reflux Two multivariate analyses posited that reflux episodes that extend proximally with mixed liquid-gas composition are significantly associated with symptoms regardless of pH status of the reflux. Weakly acidic reflux is defined as any reflux event in which the esophageal pH falls by 1 unit or more but is still less than 4 as measured by pH impedance. The mechanism by which weakly acidic or nonacid reflux may cause symptoms is not completely understood, but is thought to be a combination of mechanical distention and/or reflux contents. Two studies implicated mechanical distention by replicating heartburn symptoms with mechanical balloon dilation with esophagogastroduodenoscopy (EGD) in patients. Additionally, both bile acid and pepsin may be present in weakly acidic or nonacid reflux and may contribute to chemical irritation of the esophageal lining. Previous acid exposure likely leads to esophageal pain and hypersensitivity when exposed to weakly acidic or nonacid reflux contents regardless of pH. Future studies are warranted to further clarify the relationship between refractory GERD and weakly acidic and nonacid reflux.

Nocturnal Acid Breakthrough Nocturnal acid breakthrough (NAB) is extremely common, as it is experienced by as many as 80% of patients on twice-daily PPI therapy. One study demonstrated the efficacy of histamine-2 receptor antagonists (H2RAs) at night in conjunction with omeprazole 20 mg twice daily in almost completely eliminating NAB. However, another study showed similar symptom severity scores whether or not a patient was treated with ranitidine despite the reduction in NAB. Currently, there is insufficient evidence that NAB alone is a significant cause of refractory GERD.

Missed Gastroesophageal Reflux Disease Current testing for GERD has limitations and can lead to a missed diagnosis. Catheter-based testing can be uncomfortable and can limit typical eating patterns in patients, thus leading to uncharacteristic acid reflux patterns and increasing the potential for false-negative results. Although ambulatory pH monitoring has been shown to decrease patient discomfort, false-negative results have been reported up to 30% of the time. GERD is a chronic condition; therefore, measuring pH events over a 48-hour period likely fails to capture the chronic nature of this disease. Research has yet to elucidate the role of missed gastroesophageal reflux in symptomatic refractory GERD.

Table 1. Etiologies of Refractory GERD

<table>
<thead>
<tr>
<th>Insufficient Acid Suppression or Increased Reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PPI compliance</td>
</tr>
<tr>
<td>• PPI timing</td>
</tr>
<tr>
<td>• CYP2C19 polymorphism</td>
</tr>
<tr>
<td>• Weakly acidic reflux or nonacid reflux</td>
</tr>
<tr>
<td>• Nocturnal acid breakthrough</td>
</tr>
<tr>
<td>• Missed GERD</td>
</tr>
<tr>
<td>• Acid pocket</td>
</tr>
<tr>
<td>• Duodenogastroesophageal reflux</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Functional heartburn or reflux hypersensitivity</td>
</tr>
<tr>
<td>• Psychological comorbidities (including irritable bowel syndrome)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative Diagnoses Unrelated to GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>• Autoimmune skin conditions (eg, lichen planus)</td>
</tr>
<tr>
<td>• Pill-induced esophagitis</td>
</tr>
<tr>
<td>• Infectious esophagitis</td>
</tr>
<tr>
<td>• Caustic esophagitis</td>
</tr>
<tr>
<td>• Radiation-induced esophagitis</td>
</tr>
<tr>
<td>• Eosinophilic esophagitis</td>
</tr>
<tr>
<td>• Esophageal cancer</td>
</tr>
<tr>
<td>• Achalasia</td>
</tr>
<tr>
<td>• Gastroparesis</td>
</tr>
<tr>
<td>• <em>Helicobacter pylori</em> carrier status</td>
</tr>
<tr>
<td>• Rumination syndrome</td>
</tr>
</tbody>
</table>

CYP2C19, cytochrome P450 2C19; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.
but ongoing studies are better understanding the role of esophageal mucosal integrity testing as a more beneficial surrogate for GERD.52

**Acid Pocket**  An acid pocket refers to a postprandial collection of strong gastric acid near the gastroesophageal junction that does not mix with food. An acid pocket may migrate into the esophagus shortly after eating, causing potential reflux symptoms. PPI use can reduce the size of this pocket and increase gastric pH.53 However, it is not known how significantly, if at all, the acid pocket contributes to refractory GERD.

**Duodenogastroesophageal Reflux**  Duodenogastroesophageal reflux (DGER) refers to the reflux of duodenal contents through the stomach and into the esophagus. Bile acids may play a role in refractory GERD through either weakly acidic or nonacid reflux. More severe forms of GERD have been shown to have both acidic and bile reflux contents compared to less severe forms.54 Additionally, there is a significant association between DGER and refractory GERD, with 88% of PPI-refractory GERD patients having evidence of DGER compared to 27% of PPI responders.55

**Functional Disorders**

Functional gastrointestinal disorders are defined as symptomatic disorders without any evident organic etiology.56 Rome IV criteria define functional heartburn as episodic retrosternal pain for at least 3 months without evidence of reflux or underlying motility disorder as shown by normal EGD and normal pH testing, with a negative association between symptoms and reflux events.57 It is estimated that close to 60% of patients classified as having refractory GERD would qualify as having functional heartburn.58

The underlying mechanism of functional heartburn is not completely understood, but it is thought in part to be related to reflux hypersensitivity. This hypersensitivity is defined as increased esophageal sensitivity to various chemical, mechanical, electrical, and temperature stimuli, which may be related to enteric nervous system sensitization to acid via dilated intracellular spaces.59 Patients with refractory GERD have been shown to have increased pain sensitivity to both mechanical and electrical stimulation.60

Both functional heartburn and reflux hypersensitivity are also amplified by psychological stress.59 The exact role of psychological comorbidities in relation to refractory GERD is controversial.9 When comparing overall life stress with typical heartburn symptoms, significant life stress predicted increased heartburn severity and symptoms overall.61

**Alternative Diagnoses Unrelated to Gastroesophageal Reflux Disease**

There are several conditions unrelated to GERD that should be considered for a patient with PPI-refractory symptoms, including Zollinger-Ellison syndrome, autoimmune skin conditions, and pill-induced esophagitis (Table 1).922 The following disorders that can lead to heartburn and/or regurgitation deserve special attention.

**Eosinophilic Esophagitis**

Eosinophilic esophagitis (EoE) is an important clinical consideration in any patient with refractory GERD. Although GERD is a potential etiology and PPI use can improve EoE, there is likely also an aeroallergen or food allergen component mediated by a type 2 T helper cell cytokine release. Diagnosis is classically made by EGD with biopsy revealing more than 15 eosinophils per high-power field.62 Differentiating this condition from GERD can be challenging, as they share symptomatology, can both be associated with eosinophilia, and may both respond to PPI therapy.9 Given the increased incidence of EoE, the American College of Gastroenterology currently recommends EGD with esophageal biopsy for all patients with refractory GERD to rule out EoE.63

**Gastroparesis**

Gastroparesis is characterized by a delay of gastric emptying into the small intestine leading to increased reflux. Symptoms typically include epigastric pain, early satiety, postprandial bloating, and nausea.52 There has been a small, established association between refractory GERD and gastroparesis, with 1 study revealing that refractory GERD patients with erosive esophagitis were more likely to have delayed gastric emptying compared to patients with erosive esophagitis but no symptoms.55

**Evaluation**

If there are any alarm symptoms (eg, dysphagia, weight loss, iron deficiency anemia, bleeding), the American College of Gastroenterology recommends that these patients should first have an EGD to rule out Barrett esophagus,
stricturing disease, and malignancy, among other conditions.66 When a patient presents with typical GERD symptoms such as heartburn and reflux without alarm symptoms, it is reasonable to empirically start a single-dose PPI treatment in the morning prior to breakfast (Figure). Physicians should also pursue lifestyle modification with their patients for weight loss, smoking cessation, head-of-bed elevation, and avoidance of the right lateral decubitus position. If these interventions fail, it is important to check patient compliance with PPI therapy and ensure proper timing of its administration. If these interventions continue to fail, patients should be started on twice-daily PPI therapy. If patients remain symptomatic after 8 weeks, they would be classified as having refractory GERD and should proceed with diagnostic testing with an EGD.65

Upper Endoscopy
Endoscopy allows for visualization to determine the presence of esophagitis, which assists the physician with the differential diagnosis. It also allows for the exclusion of other disorders such as pill-induced esophagitis, EoE, stricturing disease, and malignancy. A careful initial treatment allows for a proper diagnostic approach to the patient with refractory GERD. In the absence of obvious esophagitis, biopsies of the esophagus can be helpful, especially when there is concomitant dysphagia to help rule out Barrett esophagus, lichen planus, or EoE. Careful attention to a hiatal hernia and for a possible puckered lower esophageal sphincter should be given during endoscopy to evaluate for achalasia or potential dysmotility. Evaluation of the stomach for retained foods can also help identify the potential for gastroparesis.

Reflux Testing
When there is a report of heartburn or regurgitation without obvious esophagitis on endoscopy and persistent symptoms despite PPI therapy, pH testing should be completed to determine the role of acid reflux. Whether by a catheter-based pH test or wireless pH testing placed during endoscopy, pH testing should be done off anti-reflux medications to assess the native state of gastric acid production. As mentioned previously, missed GERD is possible due to the snapshot given by these modalities. Thus, when it can be done, wireless pH capsule is preferred, as it offers 48 to 96 hours of pH monitoring with a proposed reduction of the transnasal catheter that can limit eating habits and activities, which may lead to a missed diagnosis.

Impedance-pH Testing
For patients with known GERD by prior endoscopy or pH testing with breakthrough symptoms, multichannel intraluminal impedance-pH (MII-pH) testing should be considered to evaluate the role of weakly acidic or nonacidic content. Given the established GERD diagnosis, this testing should be completed on PPI therapy to determine the role of breakthrough reflux.68 Of patients undergoing MII-pH testing, 25% will have a positive SI or SAP for nonacid reflux, which triggers their refractory GERD.10,69 However, in the majority of patients, refractory GERD is not due to acidic or nonacid reflux events based on SI or SAP.10,69 The decision to perform ambulatory pH testing vs MII-pH testing has been debated. A prospective logistic regression analysis was completed involving 471 patients; based on the predictive model, patients with refractory heartburn and failed twice-daily PPI therapy were considered to have low pretest probability for moderate to severe reflux and were recommended to undergo ambulatory pH testing off therapy.70 For patients with extraesophageal reflux, the presence of heartburn, asthma, and a body mass index greater than 25 was found to have a high probability of reflux, and these patients were recommended to undergo MII-pH testing on therapy.70

High-Resolution Esophageal Manometry
Although not a first-line test for refractory GERD, high-resolution esophageal manometry has a role in defining mimickers of GERD, including achalasia, rumination syndrome, and supragastric belching. These diagnoses are often based on patient history and examination; endoscopy can supplement this differential diagnosis, and high-resolution esophageal manometry can confirm achalasia and, if seen during the examination, can show rumination syndrome. Heartburn is seen in up to 35% of patients with achalasia and therefore should be high on the differential diagnosis for potential etiology of refractory GERD.71

Gastric Emptying Test
For patients with suspected gastroparesis, a gastric emptying test should be completed to help confirm this diagnosis. If confirmed, increasing the PPI dose is unlikely to be helpful, but dietary modifications and potential prokinetics can help improve gastric motility, which can decrease symptoms of reflux.

Medical Therapy for Partial Proton Pump Inhibitor Response

Proton Pump Inhibitors
For patients with abnormal endoscopy, pH testing, or impedance testing consistent with reflux as the etiology of symptoms, PPIs are the mainstay of therapy. As discussed previously, proper timing and compliance are key to symptom improvement. A special consideration should be made
TREATMENT OF REFRACTORY GASTROESOPHAGEAL REFLUX DISEASE

for patients with a potential CYP2C19 isoenzyme leading to rapid metabolism. Although currently this testing is not cost-effective, one strategy is to utilize medications that are not exclusively metabolized by CYP2C19 (i.e., rabeprazole or esomeprazole). For patients with partial response to PPI therapy, transitioning to CYP2C19-independent PPIs is a reasonable step (Table 2).

Histamine-2 Receptor Antagonists
H2RAs can be given to patients who have a response to PPIs and who have nighttime symptoms. Given their efficacy despite food intake, H2RAs serve as an option to reduce nighttime symptoms. In a study of 20 patients with GERD over a 28-day study period, the addition of an H2RA decreased the overall percent time of gastric pH to less than 4, but there was no difference at 2 weeks.72 Given these findings, there is a potential of tolerance to H2RAs, limiting enthusiasm for long-term efficacy.

Alginate Antacids
Alginate antacids work by forming a mechanical barrier between gastric contents and the lower esophageal sphincter when exposed to gastric acid.73,74 With this ability to form a barrier, alginate antacids have found utility in controlling postprandial heartburn and regurgitation.75 For patients with partial response to PPIs, the addition of alginate antacids serves as a useful adjunct.

Neuromodulators
For patients with reflux hypersensitivity or functional heartburn, medications aimed at decreasing the pain-processing pathways of the central nervous system can

Figure. Management algorithm for refractory symptoms of GERD.

CYP2C19, cytochrome P450 2C19; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.
help with these refractory symptoms. Both tricyclic antidepressants and selective serotonin reuptake inhibitors can decrease esophageal sensitivity. In a study comparing placebo, fluoxetine, and omeprazole for refractory GERD, fluoxetine reduced the incidence of heartburn over placebo or omeprazole.76

**Endoscopic Therapy for Refractory Gastroesophageal Reflux Disease**

**Transoral Incisionless Fundoplication**

As a method of endoscopically wrapping part of the fundus around the gastroesophageal junction, transoral incisionless fundoplication (TIF) has become the most studied endoscopic method, with randomized, controlled trial–level evidence on the management of refractory GERD. In the TEMPO study, TIF was found to be superior to high-dose PPI therapy in 60 patients defined as partial responders of PPI therapy followed at 6 months for the primary outcome of improvement of regurgitation.77 However, in the secondary outcome, both TIF and PPI use normalized esophageal acid exposure. In a subsequent randomized, controlled trial for the primary outcome of regurgitation, 87 patients were assigned to TIF and 42 patients were assigned to PPI therapy with sham surgery, with an improvement in symptoms of regurgitation seen in the TIF arm.78 Both arms showed improvement in GERD–reported outcomes; in a secondary analysis, esophageal pH improved after TIF (mean, 9.3% before and 6.3% after; \( P < .001 \)) but not after sham surgery (mean, 8.6% before and 8.9% after).78 Five-year follow-up data of the TEMPO study showed that 34% of patients were on daily PPI therapy as compared with 100% of patients at screening, which means that complete elimination of PPI use long-term postoperatively has not been shown.79 Given the improvement with PPI therapy in the TEMPO study and the need to return to PPI use following TIF in a subset of patients, the role of TIF in refractory GERD may be limited to patients with predominant regurgitation symptoms. Caution should be advised for TIF to fully eliminate the need for PPI use long term (Table 2).

**Radiofrequency Ablation**

Case series data have shown improvement in symptoms with patients with refractory GERD. In a prospective,
intention-to-treat analysis of 217 patients, radiofrequency energy delivery (Stretta, Restech) was performed with the primary outcome showing a normalization of GERD–health-related quality of life (GERD-HRQoL) in 70% or more of patients at 10 years.80 These findings are limited by lack of controlled data and lack of physiologic testing on changes in reflux. Currently, there is insufficient evidence to advocate for radiofrequency ablation in patients with refractory GERD; further studies are needed to determine its role in management and long-term efficacy when compared in prospective controlled trials with the use of physiologic pH testing.

**Surgical Therapy for Partial Proton Pump Inhibitor Response**

**Laparoscopic Fundoplication**

Laparoscopic Nissen fundoplication (LNF) is an important tool in the management of typical GERD symptoms that are responsive to PPI therapy. Predictive factors to response to antireflux surgeries include at least 50% symptom improvement with PPI therapy, compliance with antireflux medications, presence of typical symptoms of GERD, and objective findings of acid reflux.81,82 Poor response to PPI therapy is an independent risk factor for lack of response to antireflux surgery. Refractory symptoms of GERD are not always due to acid reflux, and therefore a surgical barrier to reflux does not improve symptoms. Without the aforementioned metrics for response, caution should be made for careful selection of patients with refractory GERD for antireflux surgery (Table 2).83

In a recent randomized, controlled, multicenter trial, 78 patients with reflux-induced refractory GERD were randomized to 3 arms.84 Laparoscopic fundoplication plus omeprazole (18/27 patients; 67%) was superior (as measured by the GERD-HRQL scale) to active medical treatment with bicalutamide plus omeprazole (7/25 patients; 28%; \(P<.007\)) and to control omeprazole alone for medical treatment (3/26 patients; 12%; \(P<.001\)).84

**Magnetic Sphincter Augmentation**

Minimally invasive antireflux surgeries have offered new modalities for antireflux therapy, including the magnetic sphincter augmentation (MSA; LINX, Torax Medical), which is positioned around the lower esophageal sphincter and allows bolus passage and the ability to belch as an advantage over surgical fundoplication. In a retrospective case-control series of 66 patients, 34 underwent MSA and 32 underwent LNF with the primary outcome showing improvement in GERD-HRQL (MSA, 20.6 to 5.0; LNF, 22.8 to 5.1).85 Postoperative DeMeester scores were normalized in both groups, but there was improvement in the ability to belch and in feelings of gas and bloat in MSA vs LNF.86 Limitations of broad use of MSA in refractory GERD include the lack of prospective or randomized data and lack of statistical power for a primary outcome of improvement in physiologic data, not just patient-reported outcomes.

**Summary**

Refractory GERD is a common disorder seen in both primary care and gastroenterology clinics. When symptoms occur, a thorough history can help determine alarm symptoms that necessitate endoscopy vs non–GERD-related pathology or concomitant functional esophageal disease. When symptoms are persistent, invasive testing is usually performed to evaluate for objective signs of reflux and to rule out non-GERD etiologies of symptoms of regurgitation or heartburn. Testing of reflux parameters via traditional pH testing or MII-pH testing should be considered for the evaluation of reflux or weakly acidic or nonacidic content. With predictive symptoms of partial response to PPI therapy, objective findings of reflux, possible mechanical hiatal hernia, and compliance with medications, surgical fundoplication has a role in the management of pathologic reflux with objective findings. Minimally invasive surgery and endoscopic options are novel but have yet to show long-term management of pH parameters. Importantly, the overwhelming prevalence of functional esophageal disorders with GERD should not be understated, and, in these situations, therapy directed at neuromodulation as well as behavioral therapy are more likely to have long-term efficacy and obviate the need for unnecessary surgeries or increased antireflux medicines.

The authors have no relevant conflicts of interest to disclose. Vanderbilt University Medical Center and Diversatek Healthcare jointly hold a patent on mucosal integrity testing.

**References**

Primary-care physicians’ perceptions and practices on the management of gastro-oesophageal reflux disease.


Prospective medical outpatient practice.


The criminatory power of 48-h wireless esophageal pH monitoring in the diagnosis of gastroesophageal reflux disease. 


The impact of proton pump inhibitor dosing is prevalent in patients with poorly controlled gastroesophageal reflux disease. 


The efficacy of rabeprazole on heartburn symptom resolution in patients with non-erosive and erosive gastro-oesophageal reflux disease: a multicenter study from Japan. 


Gastroenterology & Hepatology Volume 16, Issue 4 April 2020


