Treatment of Refractory Gastroesophageal Reflux Disease

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

Dr Naik is an assistant professor of medicine and Dr Vaezi is a professor of medicine, clinical director, and director of the Center for Swallowing and Esophageal Disorders in the Department of Gastroenterology, Hepatology, and Nutrition at Vanderbilt University Medical Center in Nashville, Tennessee. Dr Meyers is an internal medicine resident in the Department of Internal Medicine at Vanderbilt University Medical Center.

Address correspondence to:
Dr Rishi D. Naik
Department of Gastroenterology, Hepatology, and Nutrition
Vanderbilt University Medical Center
1660 TVC
Nashville, TN 37232-5280
Tel: 615-322-0128
Fax: 615-322-8525
E-mail: Rishi.D.Naik@vumc.org

Keywords
Gastroesophageal reflux disease, refractory gastroesophageal reflux disease, antireflux surgery, impedance testing, functional esophageal disorders, proton pump inhibitors

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).[1] 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.[2,3] In addition to a significant compromise in quality of life, potential complications of GERD include strictures, dysphagia, esophagitis, Barrett esophagus, and esophageal adenocarcinoma.[4-6]

Acid production plays a critical role in the development of heartburn.[7] Proton pump inhibitors (PPIs) decrease acid production and are the mainstay of treatment for GERD.[8] Despite the efficacy of PPI therapy, a significant percentage of patients with symptoms of GERD will not respond.[9] 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.[10] The most common presentation of GERD at an outpatient gastroenterology office visit is unresolved symptoms following failure of PPI therapy.[11,12]

Refractory symptoms of GERD are a challenging but important topic with potentially costly diagnosis, treatment, and management.[13] However, it is necessary to delineate refractory symptoms of GERD (eg, 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.[12,14] 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.[15] Both of these functional esophageal disorders are the etiology of persistent symptoms in refractory GERD in up to 90% of patients.[16] 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.[17] 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.[18]

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.[19,20] 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.[13,21,22] 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.[23] 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.[24] 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.[25] 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.[26,27] Timing of medication has also been shown to be a significant issue with PPI therapy.[28] Optimal timing is 30 to 60 minutes before meals. One study revealed that only 46% of patients dosed PPIs at appropriate times.[29] Another study reported that 36% of physicians do not give any directions or give inappropriate directions to patients regarding timing of their PPI therapy.[30] 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.[31] 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

Table 1. Etiologies of Refractory GERD

Insufficient Acid Suppression or Increased Reflux
• PPI compliance • PPI timing • CYP2C19 polymorphism • Weakly acidic reflux or nonacid reflux • Nocturnal acid breakthrough • Missed GERD • Acid pocket • Duodenogastroesophageal reflux
Functional Disorders
• Functional heartburn or reflux hypersensitivity • Psychological comorbidities (including irritable bowel syndrome)
Alternative Diagnoses Unrelated to GERD
• Zollinger-Ellison syndrome • Autoimmune skin conditions (eg, lichen planus) • Pill-induced esophagitis • Infectious esophagitis • Caustic esophagitis • Radiation-induced esophagitis • Eosinophilic esophagitis • Esophageal cancer • Achalasia • Gastroparesis • *Helicobacter pylori* carrier status • Rumination syndrome

CYP2C19, cytochrome P450 2C19; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

metabolizers, and poor metabolizers.[32] 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 (P=.047) responding effectively.[33] Furthermore, patients who were extensive metabolizers were 66% more likely to experience refractory symptoms on standard-dose PPIs compared to poor metabolizers.[33] 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.[34] There was no difference in the poor metabolizer group, suggesting that PPI metabolism may play a role in refractory GERD.[34] 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.[35]

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.[36,37] 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.[38] 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.[39,40] 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.[41,42] Previous acid exposure likely leads to esophageal pain and hypersensitivity when exposed to weakly acidic or nonacid reflux contents regardless of pH.[43] 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.[44] 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.[45] However, another study showed similar symptom severity scores whether or not a patient was treated with ranitidine despite the reduction in NAB.[46] 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.[47-49] Although ambulatory pH monitoring has been shown to decrease patient discomfort, false-negative results have been reported up to 30% of the time.[50] GERD is a chronic condition; therefore, measuring pH events over a 48-hour period likely fails to capture the chronic nature of this disease.[51,52] Research has yet to elucidate the role of missed gastroesophageal reflux in symptomatic refractory GERD,

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).[9,22] 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]

Achalasia Achalasia is a rare esophageal dysmotility disorder characterized by aperistalsis, a hypertensive lower esophageal sphincter, and inability of the lower esophageal sphincter to relax. The patient often reports dysphagia to solids and liquids, regurgitation, and sometimes heartburn. Some patients only report heartburn symptoms refractory to PPI therapy, in which the heartburn is actually retained food and liquids above the lower esophageal sphincter. This diagnosis can be made with EGD and can be confirmed by esophageal manometry.[64]

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.[22] 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.[65]

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.[67] 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.[63]

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 antireflux 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

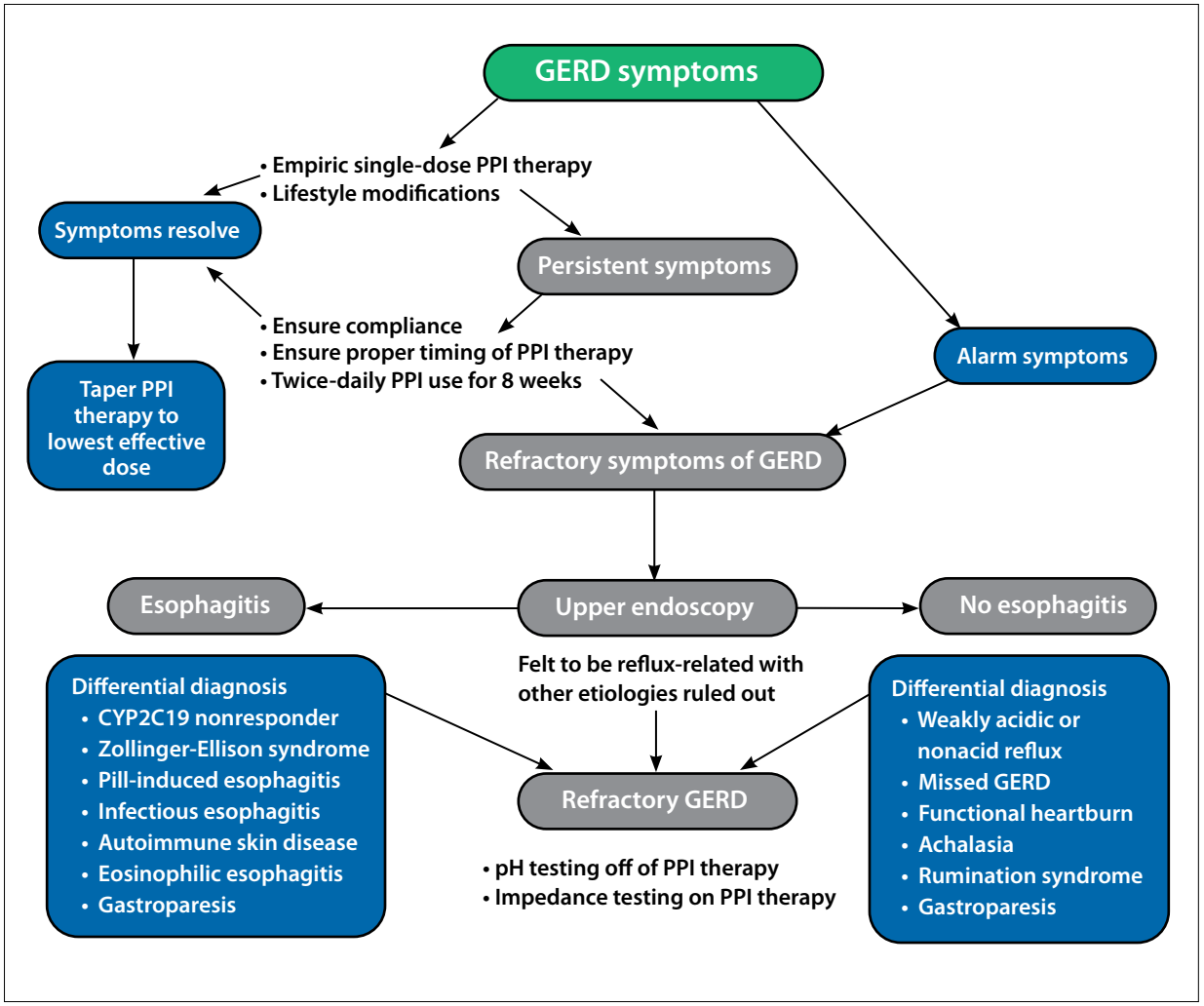

Figure. Management algorithm for refractory symptoms of GERD.

CYP2C19, cytochrome P450 2C19; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

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 (ie, 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

Table 2. Advantages and Disadvantages of Treatment of Refractory GERD and Partial PPI Response

	Method	Advantage(s)	Disadvantage(s)
Medical	PPIs	Easily accessible	Increased risk of enteric infections; CYP2C19 polymorphism
	H2RAs	Not dependent on timing with food	Tolerance can build with continued use
	Alginate antacids	Improved postprandial heartburn and regurgitation	Do not reduce acidic content
	Neuromodulators	Treat overlap of functional esophageal disorders	Potential drug interactions
Endoscopic	Transoral incisionless fundoplication	RCT-level evidence of 6-month improvement in regurgitation	At 5 years, return of PPI use in a subset of patients
	Radiofrequency ablation	Improvement of GERD–health-related quality of life	No controlled studies
Surgical	Laparoscopic fundoplication	Improvement in both heartburn and correction of large hiatal hernias; RCT evidence of superiority over medical therapy	Increase in gas-bloat symptoms, dysphagia
	Magnetic sphincter augmentation	Improvement in GERD–health-related quality of life and regurgitation; improved ability for belching compared to laparoscopic fundoplication	Data limited to patient-reported outcome, not change in physiologic parameters; migration; esophageal perforation; dysphagia

CYP2C19, cytochrome P450 2C19; GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; RCT, randomized, controlled trial.

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-HRQL) 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 baclofen 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.[85] 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

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101(8):1900-1920.
2. Yamasaki T, Hemond C, Eisa M, Ganocy S, Fass R. The changing epidemiology of gastroesophageal reflux disease: are patients getting younger? *J Neurogastroenterol Motil*. 2018;24(4):559-569.
3. Richter JE, Rubenstein JH. Presentation and epidemiology of gastroesophageal reflux disease. *Gastroenterology*. 2018;154(2):267-276.
4. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012;143(5):1179-1187.e3.
5. Subramanian CR, Triadafilopoulos G. Refractory gastroesophageal reflux disease. *Gastroenterol Rep (Oxf)*. 2015;3(1):41-53.
6. DiPalma JA. Management of severe gastroesophageal reflux disease. *J Clin Gastroenterol*. 2001;32(1):19-26.
7. Smith JL, Opekun AR, Larkai E, Graham DY. Sensitivity of the esophageal mucosa to pH in gastroesophageal reflux disease. *Gastroenterology*. 1989;96(3):683-689.

8. Strand DS, Kim D, Peura DA. 25 years of proton pump inhibitors: a comprehensive review. *Gut Liver*. 2017;11(1):27-37.
9. Mermelstein J, Chait Mermelstein A, Chait MM. Proton pump inhibitor-refractory gastroesophageal reflux disease: challenges and solutions. *Clin Exp Gastroenterol*. 2018;11:119-134.
10. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. *Gut*. 2012;61(9):1340-1354.
11. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease—where next? *Aliment Pharmacol Ther*. 2005;22(2):79-94.
12. Dean BB, Gano AD Jr, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol*. 2004;2(8):656-664.
13. Hershcovici T, Fass R. Step-by-step management of refractory gastresophageal reflux disease. *Dis Esophagus*. 2013;26(1):27-36.
14. Miwa H, Sasaki M, Furuta T, et al; Acid-Related Symptom (ARS) Research Group. Efficacy of rabeprazole on heartburn symptom resolution in patients with non-erosive and erosive gastro-oesophageal reflux disease: a multicenter study from Japan. *Aliment Pharmacol Ther*. 2007;26(1):69-77.
15. Ang D, Teo EK, Ang TL, et al. To Bravo or not? A comparison of wireless esophageal pH monitoring and conventional pH catheter to evaluate non-erosive gastroesophageal reflux disease in a multiracial Asian cohort. *J Dig Dis*. 2010;11(1):19-27.
16. Gyawali CP, Fass R. Management of gastroesophageal reflux disease. *Gastroenterology*. 2018;154(2):302-318.
17. Abdallah J, George N, Yamasaki T, Ganocy S, Fass R. Most patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy also have functional esophageal disorders. *Clin Gastroenterol Hepatol*. 2019;17(6):1073-1080.e1.
18. Fass OZ, Fass R. Overlap between GERD and functional esophageal disorders—a pivotal mechanism for treatment failure. *Curr Treat Options Gastroenterol*. 2019;17(1):161-164.
19. Kahrilas PJ, Jonsson A, Denison H, Wernersson B, Hughes N, Howden CW. Regurgitation is less responsive to acid suppression than heartburn in patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2012;10(6):612-619.
20. Kahrilas PJ, Howden CW, Hughes N. Response of regurgitation to proton pump inhibitor therapy in clinical trials of gastroesophageal reflux disease. *Am J Gastroenterol*. 2011;106(8):1419-1425.
21. Hershcovici T, Fass R. An algorithm for diagnosis and treatment of refractory GERD. *Best Pract Res Clin Gastroenterol*. 2010;24(6):923-936.
22. Richter JE. How to manage refractory GERD. *Nat Clin Pract Gastroenterol Hepatol*. 2007;4(12):658-664.
23. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology*. 2008;135(4):1383-1391, 1391.e1-e5.
24. Herregods TV, Troelstra M, Weijenborg PW, Bredenoord AJ, Smout AJ. Patients with refractory reflux symptoms often do not have GERD. *Neurogastroenterol Motil*. 2015;27(9):1267-1273.
25. Van Soest EM, Siersema PD, Dieleman JP, Sturkenboom MC, Kuipers EJ. Persistence and adherence to proton pump inhibitors in daily clinical practice. *Aliment Pharmacol Ther.* 2006;24(2):377-385.
26. Bredenoord AJ, Smout AJ. Refractory gastrooesophageal reflux disease. *Eur J Gastroenterol Hepatol*. 2008;20(3):217-223.
27. Gosselin A, Luo R, Lohoues H, et al. The impact of proton pump inhibitor compliance on health-care resource utilization and costs in patients with gastroesophageal reflux disease. *Value Health*. 2009;12(1):34-39.
28. Hungin AP, Rubin G, O'Flanagan H. Factors influencing compliance in long-term proton pump inhibitor therapy in general practice. *Br J Gen Pract*. 1999;49(443):463-464.
29. Gunaratnam NT, Jessup TP, Inadomi J, Lascewski DP. Sub-optimal proton pump inhibitor dosing is prevalent in patients with poorly controlled gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 2006;23(10):1473-1477.
30. Chey WD, Inadomi JM, Booher AM, Sharma VK, Fendrick AM, Howden CW. Primary-care physicians' perceptions and practices on the management of GERD: results of a national survey. *Am J Gastroenterol.* 2005;100(6):1237-1242.
31. Barrison AF, Jarboe LA, Weinberg BM, Nimmagadda K, Sullivan LM, Wolfe MM. Patterns of proton pump inhibitor use in clinical practice. *Am J Med*. 2001;111(6):469-473.
32. Furuta T, Shirai N, Watanabe F, et al. Effect of cytochrome P4502C19 genotypic differences on cure rates for gastroesophageal reflux disease by lansoprazole. *Clin Pharmacol Ther.* 2002;72(4):453-460.
33. Ichikawa H, Sugimoto M, Sugimoto K, Andoh A, Furuta T. Rapid metabolizer genotype of CYP2C19 is a risk factor of being refractory to proton pump inhibitor therapy for reflux esophagitis. *J Gastroenterol Hepatol.* 2016;31(4):716-726.
34. Chen WY, Chang WL, Tsai YC, Cheng HC, Lu CC, Sheu BS. Double-dosed pantoprazole accelerates the sustained symptomatic response in overweight and obese patients with reflux esophagitis in Los Angeles grades A and B. *Am J Gastroenterol*. 2010;105(5):1046-1052.
35. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. *Expert Opin Drug Metab Toxicol.* 2018;14(4):447-460.
36. Tutuian R, Vela MF, Hill EG, Mainie I, Agrawal A, Castell DO. Characteristics of symptomatic reflux episodes on acid suppressive therapy. *Am J Gastroenterol.* 2008;103(5):1090-1096.
37. Zerbib F, Duriez A, Roman S, Capdepont M, Mion F. Determinants of gastro-oesophageal reflux perception in patients with persistent symptoms despite proton pump inhibitors. *Gut.* 2008;57(2):156-160.
38. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut*. 2004;53(7):1024-1031.
39. Takeda T, Nabae T, Kassab G, Liu J, Mittal RK. Oesophageal wall stretch: the stimulus for distension induced oesophageal sensation. *Neurogastroenterol Motil.* 2004;16(6):721-728.
40. de Caestecker JS, Pryde A, Heading RC. Site and mechanism of pain perception with oesophageal balloon distension and intravenous edrophonium in patients with oesophageal chest pain. *Gut.* 1992;33(5):580-586.
41. Vaezi MF, Lacamera RG, Richter JE. Validation studies of Bilitec 2000: an ambulatory duodenogastric reflux monitoring system. *Am J Physiol.* 1994;267(6 pt 1):G1050-G1057.
42. Pearson JP, Parikh S, Orlando RC, et al. Review article: reflux and its consequences—the laryngeal, pulmonary and oesophageal manifestations. Conference held in conjunction with the 9th International Symposium on Human Pepsin (ISHP) Kingston-upon-Hull, UK, 21-23 April 2010. *Aliment Pharmacol Ther.* 2011;33(suppl 1):1-71.
43. Emerenziani S, Ribolsi M, Guarino MP, et al. Acid reflux episodes sensitize the esophagus to perception of weakly acidic and mixed reflux in non-erosive reflux disease patients. *Neurogastroenterol Motil.* 2014;26(1):108-114.
44. Xue S, Katz PO, Banerjee P, Tutuian R, Castell DO. Bedtime H2 blockers improve nocturnal gastric acid control in GERD patients on proton pump inhibitors. *Aliment Pharmacol Ther.* 2001;15(9):1351-1356.
45. Peghini PL, Katz PO, Castell DO. Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: a controlled study in normal subjects. *Gastroenterology.* 1998;115(6):1335-1339.
46. Orr WC, Harnish MJ. The efficacy of omeprazole twice daily with supplemental H2 blockade at bedtime in the suppression of nocturnal oesophageal and gastric acidity. *Aliment Pharmacol Ther*. 2003;17(12):1553-1558.
47. Iluyomade A, Olowoyeye A, Fadahunsi O, et al. Interference with daily activities and major adverse events during esophageal pH monitoring with bravo wireless capsule versus conventional intranasal catheter: a systematic review of randomized controlled trials. *Dis Esophagus.* 2017;30(3):1-9.
48. Saritas Yuksel E, Higginbotham T, Slaughter JC, et al. Use of direct, endoscopic-guided measurements of mucosal impedance in diagnosis of gastroesophageal reflux disease. *Clin Gastroenterol Hepatol.* 2012;10(10):1110-1116.
49. Kahrilas PJ, Shaheen NJ, Vaezi MF; American Gastroenterological Association Institute; Clinical Practice and Quality Management Committee. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology.* 2008;135(4):1392-1413, 1413.e1-e5.
50. Tseng D, Rizvi AZ, Fennerty MB, et al. Forty-eight-hour pH monitoring increases sensitivity in detecting abnormal esophageal acid exposure. *J Gastrointest Surg.* 2005;9(8):1043-1051.
51. Wenner J, Johansson J, Johnsson F, Oberg S. Optimal thresholds and discriminatory power of 48-h wireless esophageal pH monitoring in the diagnosis of GERD. *Am J Gastroenterol*. 2007;102(9):1862-1869.
52. Patel DA, Higginbotham T, Slaughter JC, et al. Development and validation of a mucosal impedance contour analysis system to distinguish esophageal disorders. *Gastroenterology.* 2019;156(6):1617-1626.e1.
53. Boeckxstaens G. The relationship between the acid pocket and GERD. *Gastroenterol Hepatol (N Y).* 2013;9(9):595-596.
54. Vaezi MF, Richter JE. Importance of duodeno-gastro-esophageal reflux in the medical outpatient practice. *Hepatogastroenterology.* 1999;46(25):40-47.
55. Kunsch S, Neesse A, Linhart T, Nell C, Gress TM, Ellenrieder V. Prospective

evaluation of duodenogastroesophageal reflux in gastroesophageal reflux disease patients refractory to proton pump inhibitor therapy. *Digestion*. 2012;86(4):315-322.
56. Whitfield KL, Shulman RJ. Treatment options for functional gastrointestinal disorders: from empiric to complementary approaches. *Pediatr Ann.* 2009;38(5):288-290, 292-294.
57. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV [published online February 19, 2016]. *Gastroenterology.* doi:10.1053/j.gastro.2016.02.032.
58. Yamasaki T, O'Neil J, Fass R. Update on functional heartburn. *Gastroenterol Hepatol (N Y).* 2017;13(12):725-734.
59. Miwa H, Kondo T, Oshima T, Fukui H, Tomita T, Watari J. Esophageal sensation and esophageal hypersensitivity—overview from bench to bedside. *J Neurogastroenterol Motil.* 2010;16(4):353-362.
60. Hershcovici T, Fass R. Nonerosive reflux disease (NERD)—an update. *J Neurogastroenterol Motil.* 2010;16(1):8-21.
61. Naliboff BD, Mayer M, Fass R, et al. The effect of life stress on symptoms of heartburn. *Psychosom Med.* 2004;66(3):426-434.
62. O'Shea KM, Aceves SS, Dellon ES, et al. Pathophysiology of eosinophilic esophagitis. *Gastroenterology.* 2018;154(2):333-345.
63. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013;108(3):308-328.
64. Islam S. Achalasia. *Semin Pediatr Surg.* 2017;26(2):116-120.
65. Dickman R, Boaz M, Aizic S, Beniashvili Z, Fass R, Niv Y. Comparison of clinical characteristics of patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy versus those who fully responded. *J Neurogastroenterol Motil.* 2011;17(4):387-394.
66. Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. *World J Gastrointest Pharmacol Ther.* 2014;5(3):105-112.
67. Kang JH, Kang JY. Lifestyle measures in the management of gastro-oesophageal reflux disease: clinical and pathophysiological considerations. *Ther Adv Chronic Dis.* 2015;6(2):51-64.
68. Vela MF. Non-acid reflux: detection by multichannel intraluminal impedance and pH, clinical significance and management. *Am J Gastroenterol.* 2009;104(2):277-280.
69. Zerbib F, Sifrim D, Tutuian R, Attwood S, Lundell L. Modern medical and surgical management of difficult-to-treat GORD. *United European Gastroenterol J.* 2013;1(1):21-31.
70. Patel DA, Sharda R, Choksi YA, et al. Model to select on-therapy vs off-therapy tests for patients with refractory esophageal or extraesophageal symptoms. *Gastroenterology.* 2018;155(6):1729-1740.e1.
71. Ponce J, Ortiz V, Maroto N, Ponce M, Bustamante M, Garrigues V. High prevalence of heartburn and low acid sensitivity in patients with idiopathic achalasia. *Dig Dis Sci.* 2011;56(3):773-776.
72. Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. *Gastroenterology.* 2002;122(3):625-632.
73. Mandel KG, Deggi BP, Brodi DA, Jeykobi GI. Alginate-raft preparations in the treatment of acid reflux and heartburn (literature review) [in German]. *Eksp Klin Gastroenterol.* 2008;(4):64-77.
74. Zentilin P, Dulbecco P, Savarino E, et al. An evaluation of the antireflux properties of sodium alginate by means of combined multichannel intraluminal impedance and pH-metry. *Aliment Pharmacol Ther.* 2005;21(1):29-34.
75. Rohof WO, Bennink RJ, Smout AJ, Thomas E, Boeckxstaens GE. An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol.* 2013;11(12):1585-1591.
76. Ostovaneh MR, Saeidi B, Hajifathalian K, et al. Comparing omeprazole with fluoxetine for treatment of patients with heartburn and normal endoscopy who failed once daily proton pump inhibitors: double-blind placebo-controlled trial. *Neurogastroenterol Motil.* 2014;26(5):670-678.
77. Trad KS, Barnes WE, Simoni G, et al. Transoral incisionless fundoplication effective in eliminating GERD symptoms in partial responders to proton pump inhibitor therapy at 6 months: the TEMPO randomized clinical trial. *Surg Innov.* 2015;22(1):26-40.
78. Hunter JG, Kahrilas PJ, Bell RC, et al. Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. *Gastroenterology.* 2015;148(2):324-333.e5.
79. Trad KS, Barnes WE, Prevou ER, et al. The TEMPO trial at 5 years: transoral fundoplication (TIF 2.0) is safe, durable, and cost-effective. *Surg Innov.* 2018;25(2):149-157.
80. Noar M, Squires P, Khan S. Radiofrequency energy delivery to the lower esophageal sphincter improves gastroesophageal reflux patient-reported outcomes in failed laparoscopic Nissen fundoplication cohort. *Surg Endosc.* 2017;31(7):2854-2862.
81. Hayden J, Jamieson G. Optimization of outcome after laparoscopic antireflux surgery. *ANZ J Surg.* 2006;76(4):258-263.
82. Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg.* 1999;3(3):292-300.
83. Lundell L, Bell M, Ruth M. Systematic review: laparoscopic fundoplication for gastroesophageal reflux disease in partial responders to proton pump inhibitors. *World J Gastroenterol.* 2014;20(3):804-813.
84. Spechler SJ, Hunter JG, Jones KM, et al. Randomized trial of medical versus surgical treatment for refractory heartburn. *N Engl J Med.* 2019;381(16):1513-1523.
85. Louie BE, Farivar AS, Shultz D, Brennan C, Vallières E, Aye RW. Short-term outcomes using magnetic sphincter augmentation versus Nissen fundoplication for medically resistant gastroesophageal reflux disease. *Ann Thorac Surg.* 2014;98(2):498-504.