

Management of Gastroesophageal Reflux Disease

C. Prakash Gyawali¹Ronnie Fass²

¹Division of Gastroenterology, Washington University School of Medicine, St. Louis, Missouri; and ²Division of Gastroenterology and Hepatology, Esophageal and Swallowing Center, Case Western Reserve University, MetroHealth Medical Center, Cleveland, Ohio

Management of gastroesophageal reflux disease (GERD) commonly starts with an empiric trial of proton pump inhibitor (PPI) therapy and complementary lifestyle measures, for patients without alarm symptoms. Optimization of therapy (improving compliance and timing of PPI doses), or increasing PPI dosage to twice daily in select circumstances, can reduce persistent symptoms. Patients with continued symptoms can be evaluated with endoscopy and tests of esophageal physiology, to better determine their disease phenotype and optimize treatment. Laparoscopic fundoplication, magnetic sphincter augmentation, and endoscopic therapies can benefit patients with well-characterized GERD. Patients with functional diseases that overlap with or mimic GERD can be treated with neuromodulators (primarily antidepressants), or psychological interventions (psychotherapy, hypnotherapy, cognitive behavioral therapy). Future approaches to treatment of GERD include potassium-competitive acid blockers, reflux-reducing agents, bile acid binders, injection of inert substances into the esophagogastric junction, and electrical stimulation of the lower esophageal sphincter.

Keywords: Gastroesophageal Reflux Disease; Proton Pump Inhibitor; Histamine-2 Receptor Antagonist; Antireflux Surgery.

Gastroesophageal reflux disease (GERD) is a common diagnosis for all age groups and both sexes, with estimated prevalence rates of 8% to 33% worldwide.¹ The economic burden is \$9 to \$10 billion per year in direct costs in the United States alone, mainly related to use of proton pump inhibitors (PPIs).² PPIs are prescribed empirically as a pragmatic initial diagnostic approach for patients with typical symptoms of GERD,^{3,4} as well as atypical symptoms (noncardiac chest pain, chronic cough, hoarseness, throat clearing, wheezing). Sometimes, patients are given double the standard dose; overprescription and inappropriate use of PPIs is a widespread problem.⁵

Esophageal testing can stratify patients with GERD into management categories for appropriate use of antireflux

therapy. The presence of erosive esophagitis is associated with response to antireflux therapy.⁶ Additionally, increased distal esophageal acid exposure time (AET) predicts symptom improvement following antireflux therapy; positive symptom association probability complements increased AET in this setting.^{6,7} Using these 2 parameters, GERD can be characterized into distinct phenotypes that have management implications.⁸ More than two-thirds of patients with increased AET have a symptomatic response to medical or surgical antireflux therapy.⁸ On the other hand, physiologic reflux metrics indicate a functional basis for symptoms,^{9,10} and fewer than 50% of patients with physiologic reflux burden and negative symptom-reflux association report reduced symptoms. When symptoms associate with reflux episodes in patients with physiologic reflux (reflux hypersensitivity), treatment outcomes vary. We review management strategies for GERD and approaches to GERD symptoms that persist despite seemingly adequate disease management.

Management

Lifestyle

Lifestyle measures designed to reduce reflux symptoms are typically initiated at presentation, and should be recommended for all patients with GERD. Unfortunately, many physicians either do not provide clear instructions for lifestyle modifications or offer patients a printed list of activities and food items to avoid, which patients find hard

Abbreviations used in this paper: AET, acid exposure time; ARS, antireflux surgery; BE, Barrett's esophagus; EGJ, esophagogastric junction; GERD, gastroesophageal reflux disease; H2RA, H₂ receptor antagonists; LES, lower esophageal sphincter; MSA, magnetic sphincter augmentation; NERD, nonerosive reflux disease; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; RFA, radiofrequency application; TIF, transoral incisionless fundoplication; TLESR, transient LES relaxation.

Most current article

© 2018 by the AGA Institute
0016-5085/\$36.00

<https://doi.org/10.1053/j.gastro.2017.07.049>

to follow.¹¹ Some patients report specific foods that induce GERD symptoms, including citrus, spicy food, caffeine, chocolate, and fatty foods. However, broad dietary restrictions are of limited value in reducing esophageal symptoms.¹²

The association between weight gain and GERD symptoms is well established in population studies; weight gain has also been associated with increased risk of erosive esophagitis and Barrett's esophagus (BE).^{13–15} Even modest weight gain can exacerbate GERD symptoms in both non-obese and obese individuals, particularly women.¹⁶ Consequently, weight loss and reduction in waist circumference has been demonstrated to reduce symptoms of GERD, esophageal acid exposure, and post-prandial reflux events.^{17–20}

Because nighttime breakthrough symptoms are commonly reported by patients failing GERD therapy,²¹ emphasizing lifestyle modifications for nighttime hours is especially important. Sleeping with the head end of the bed elevated, using either blocks under bedposts or a wedge, reduces reflux episodes, with faster acid clearance and fewer reflux symptoms compared with sleeping flat.¹² AET is longer, and acid clearance is slower when lying on the right side compared with the left, possibly because the esophagogastric junction (EGJ) is above the level of pooled acid while lying on the left side.^{22–24} Other measures include turning off bedroom lights and minimizing disturbances to normal sleep.²⁵ Despite associations between post-prandial reflux episodes and GERD symptoms, there is no conclusive evidence that avoiding late-night meals reduces esophageal acid burden.²⁶

Although smokers have more reflux symptoms,^{27,28} there is no evidence that smoking cessation consistently reduces esophageal acid exposure or GERD symptoms.^{29,30} Similarly, alcohol use can induce reflux symptoms,^{31,32} but alcohol abstinence does not decrease esophageal reflux burden.³³ Despite lack of conclusive evidence, there are health benefits to cessation of smoking and alcohol use, particularly in reducing neoplastic progression of BE and risk of esophageal adenocarcinoma.^{34,35}

PPIs

PPIs are the mainstay of medical management of GERD, due to irreversible blockade of the activated $H^+ K^+$ ATPase proton pump in the gastric parietal cells. Effects are not immediate because the PPI needs to concentrate in the acidic secretory canaliculi of the parietal cell before inhibiting the proton pump.³⁶ Acid production is suppressed until new proton pumps regenerate, so the PPI is readministered each day, to ensure continued acid suppression. PPIs do not affect pathophysiologic mechanisms of reflux or reduce numbers of reflux events; instead they alter the pH of the refluxate to weakly acidic or alkaline.³⁷ For optimal efficacy, PPIs should be taken 30 to 45 minutes before meals. A meta-analysis of studies evaluating various formulations of PPIs found negligible differences in efficacy between PPIs in healing erosive esophagitis or in symptom relief.³⁸ There is no clear benefit to escalating the dose beyond twice daily.

The concept of proven vs unproven GERD determines who needs esophageal testing before long-term acid-suppressive therapy is contemplated.⁶ An abnormal pH test and/or

erosive esophagitis or BE on upper endoscopy defines proven GERD; GERD remains unproven when these have not been demonstrated. Best practice recommendations for proven GERD consist of long-term therapy with the lowest dose of PPI that provides symptom control and/or healing of esophagitis.³⁹ In contrast, patients with unproven GERD, or those with atypical esophageal symptoms and normal endoscopy, benefit from esophageal reflux monitoring to define abnormal reflux burden before initiation of long-term PPI therapy. Therefore, the clinician managing GERD needs to address indication, consider evidence of efficacy for the indication, and establish benefit over risk before initiating long-term PPI therapy.⁴⁰

Typical symptoms of GERD are reduced with PPI therapy. This led to the development of the PPI trial,⁴¹ in lieu of esophageal tests for patients with heartburn without alarm symptoms. A meta-analysis showed that the sensitivity of a 7-day PPI trial in resolving heartburn was 71% in the presence of erosive esophagitis, and 78% when ambulatory pH monitoring was abnormal⁴²; however, specificity was suboptimal at 41% and 54%, respectively, implying a mixture of GERD and non-GERD mechanisms underlying uninvestigated heartburn.⁴³

Abnormal esophageal acid burden correlates with response of symptoms to the PPI trial (odds ratio 4.11).⁴⁴ Meta-analyses have found that 72% of patients with erosive esophagitis respond to PPI therapy, and 73.5% of patients with nonerosive reflux disease (NERD) confirmed by abnormal reflux monitoring.⁴³ In contrast, fewer than 47% of patients with functional heartburn and reflux hypersensitivity respond to PPI therapy.^{8,9,45} Symptom-reflux association alone has not been consistently associated with treatment outcome, compared with the presence of erosive esophagitis or abnormal AET.^{7,8,46–48}

Short-term PPI therapy heals esophagitis in 72% to 83% of patients (compared with 18% to 20% for placebo, see Table 1),^{43,49} but resolves heartburn in only 56% to 77% of patients with esophagitis (with 4–12 weeks of therapy).^{50–52} PPIs maintain healing of erosive esophagitis in 93% of patients (compared with 29% of patients for placebo),⁵³ and lower doses may suffice. The standard dose of PPIs resolves heartburn in only 37% to 61% of patients without erosive esophagitis or with uninvestigated heartburn (Table 1).^{43,52,54} Thus, patients with a nonresponse or incomplete response to PPIs should undergo esophageal evaluation to confirm the presence or absence of GERD as a cause of symptoms.⁶ The optimal indications for PPI therapy, therefore, consist of erosive esophagitis and NERD with abnormal ambulatory reflux parameters.

In contrast to patients with heartburn, PPIs reduce symptoms in only 26% to 64% of patients with regurgitation,^{55,56} only 17% more patients than those receiving placebo.^{55,56} Response rates are even lower with patients with atypical symptoms of GERD, indicating differences in mechanisms of pathogenesis. Among patients with atypical symptoms, those with GERD-related noncardiac chest pain have the best response to PPIs,^{48,57} with sensitivity of 84% and specificity of 74% in predicting reflux etiology when symptoms respond.^{58,59} Symptoms are reduced by

Table 1. Responses of GERD Symptoms and Esophagitis to Acid Suppression in Randomized Controlled Trials

	Response to treatment, %	Response to placebo, %	Risk ratio for response (95% confidence interval)	Number needed to treat
Proton pump inhibitors				
Uninvestigated heartburn ⁵⁵	70.3	25.1	2.80 (2.25–3.50)	2.2
Heartburn without esophagitis ⁵⁵	39.7	12.6	3.15 (2.71–3.67)	3.7
Heartburn with esophagitis ⁵³	55.5	7.5	6.93 (3.55–13.52)	2.1
Erosive esophagitis ⁵⁰	85.6	28.3	2.96 (2.14–4.11)	1.8
Regurgitation ⁵⁶	64.0	46.4	1.40 (1.29–1.47)	5.7
Noncardiac chest pain, positive GERD testing ⁵⁸	74.5	17.2	4.33 (3.04–6.18)	1.7
Noncardiac chest pain, negative GERD testing ⁵⁸	23.6	28.2	0.84 (0.54–1.31)	22.0
Chronic cough ⁶¹	18.1	9.3	1.94 (0.87–4.34)	11.4
Laryngeal symptoms ⁶²	14.7	16	0.92 (0.41–2.05)	79.2
Histamine-2 Receptor Antagonists				
Uninvestigated heartburn ⁵⁵	54.6	40.6	1.34 (1.18–1.53)	7.1
Heartburn without esophagitis ⁵⁵	35.4	22.0	1.61 (1.15–2.26)	7.5
Erosive esophagitis ⁵⁰	41.0	20.3	2.10 (1.30–3.24)	4.8

longer-term PPI therapy in 56% to 85% of patients with noncardiac chest pain with GERD evidence on ambulatory reflux monitoring, but in only 0% to 17% of patients without objective evidence for GERD.⁵⁷ Fewer patients with cough⁶⁰ and laryngeal symptoms⁶¹ respond to PPI treatment (fewer than 25%), even when results from ambulatory reflux monitoring are abnormal. Chronic cough can improve (but not always resolve) with PPI therapy in patients with objective evidence for GERD.^{60,62} PPIs and placebo resolve laryngeal symptoms in similar proportions of patients without heartburn.⁶¹ In asthmatic individuals, PPIs can improve peak expiratory flow in select patients (heartburn associated with asthma symptoms, erosive esophagitis, or BE) with nocturnal respiratory symptoms.⁶³

On-demand PPI therapy may reduce the pill burden for patients, but may lead to suboptimal satisfaction with management compared with continuous PPI therapy.⁶⁴ Esophageal pH monitoring in patients with well-established GERD demonstrated increased acid burden on days when PPIs were not taken, compared with continuous therapy.⁶⁵ Reducing PPI dosing to alternate day or on-demand should be considered on a case-by-case basis; this is most likely to benefit patients without high-grade erosive esophagitis or other complications of GERD, such as BE or peptic strictures.

Long-term use of PPIs has been linked to various adverse effects in large population-based studies, including reduction in micronutrient absorption, gastrointestinal and pulmonary infections, osteoporosis and bone fractures, heart disease, kidney disease, and dementia (Table 2).^{66,67} However, no well-designed prospective studies have evaluated cause and effect between PPI use and these adverse effects.⁶⁸ Evidence and expert opinions concur that PPI use, including short-term use of over-the-counter PPIs, does not mask symptoms of serious diseases such as gastrointestinal cancers.^{40,66,69} Also, routine monitoring of micronutrients is not necessary for most patients. PPIs have clear advantages in treatment of syndromes with mucosal damage or typical presentations of GERD. The PPI-first approach has been shown to be cost-effective,⁷⁰ followed by a step-down approach that

incorporates H₂ receptor antagonists (H2RAs) for patients with symptomatic GERD resolved by PPIs.⁷¹

H2RAs

H2RAs block acid secretion by competing for histamine receptors in the gastric parietal cell. H2RAs lead to healing in 41% of patients with esophagitis, compared with 18% to 20% on placebo^{43,49}; heartburn resolves in 48% to 56% of patients after 4 to 12 weeks of H2RA treatment (Table 1).^{50–52} There is a relationship between H2RA dose and degree of esophageal healing; higher doses are more effective than lower doses.⁷² However, doses higher than twice-daily H2RA do not provide better healing or symptom control. In general, H2RAs are less effective than PPI therapy.⁵⁴

H2RAs are mostly used as part of a step-down treatment for patients with uncomplicated symptoms of GERD following PPI-induced remission of symptoms. As many as a third of patients with symptomatic heartburn can be successfully converted to H2RA therapy, whereas 15% can go off all acid-suppressive medications.⁷¹ However, 42% of patients must return to PPI therapy for symptom relief. Step-down therapy is generally only recommended for patients without erosive esophagitis or BE; in these patients, the value of continued PPI therapy is considered to be more significant than that of H2RA therapy.

The addition of H2RA to PPI regimens might improve control of gastric acid, with more prolonged duration of intragastric pH >4 compared with PPI alone.⁷³ H2RAs have therefore been used as an adjunct to PPI regimens for patients whose symptoms do not respond adequately to PPI therapy. Although studies demonstrated suppression of nocturnal acid with supplemental H2RAs administered at bedtime,⁷⁴ this is associated with rapid tachyphylaxis (within 7 days), and long-term acid control is similar for patients on PPIs with vs without an H2RA.⁷⁵

Reflux-Reducing Agents

Baclofen, a gamma-amino butyric acid B receptor agonist, reduces transient lower esophageal sphincter (LES)

Table 2. Risks of Long-term Proton Pump Inhibitor Therapy

Potential adverse event	Relative risk	Absolute excess risk	Strength of evidence	Consistency of evidence	Comments
<i>Clostridium difficile</i> infection	As much as a threefold increase	0–0.09 per patient/y	Moderate	No	OR 2.10 (1.20–3.50)
Bacterial gastroenteritis	Twofold to sixfold increase	0.3%–0.2% per patient/y	Moderate	Yes	OR 3.33 (1.84–6.02); weaker association with H2RA: OR 2.03 (1.05–3.92)
Small intestinal bacterial overgrowth	Twofold to eightfold increase		Weak	No	OR 2.28 (1.23–4.21)
Spontaneous bacterial peritonitis	As much as a threefold increase	3%–16% per patient/y	Weak	No	OR 2.17 (1.46–3.23)
Pneumonia	No association observed in RCTs		Weak	No	OR 1.49 (1.16–1.92) on observational studies; unproven causality
Chronic kidney disease	10%–20% increase	0.1%–0.3% per patient/y	Weak	No	Acute interstitial nephritis (idiosyncratic reaction, proven cause): OR 5.16 (2.21–12.05); chronic kidney injury (unproven causality): OR 1.50 (1.14–1.96)
Bone fracture	As much as a fourfold increase	0.1%–0.5% per patient/y	Weak	No	OR 1.44 (1.30–1.59) with use >1 year in duration; unproven cause; no tendency towards osteoporosis on studies of bone mineral density
Dementia	4%–80% increase	0.07%–1.5% per patient/y	Weak	No	HR 1.44 (1.36–1.52); unproven cause
Myocardial infarction	No association found in RCTs		Weak	No	HR 1.16 (1.09–1.24) in observational studies
Gastrointestinal malignancies	No association found in RCTs				Benign fundic gland polyps: OR 2.2 (1.3–3.8)
Micronutrient deficiencies	60%–70% increase	0.3%–0.4% per patient/y	Weak	No	Vitamin B12 deficiency: OR 1.65 (1.58–1.73); iron deficiency: OR 2.49 (2.35–2.64)
Hypomagnesemia	Case reports		Weak	Yes	OR 1.78 (1.01–2.92); idiosyncratic reaction

Data from Freedberg et al,⁴⁰ Vaezi et al,⁶⁹ Scarpignato et al,⁶⁸ Kia et al,⁷⁰ and Yadlapati et al.⁴¹

CI, confidence interval; H2RA, histamine 2 receptor antagonists; HR, hazard ratio; OR, odds ratio; RCT, randomized controlled trial.

relaxations (TLESRs), and reduces reflux events in healthy volunteers as well as patients with GERD.⁷⁶ However, baclofen is associated with central side effects (somnolence, dizziness) that may limit its usefulness.⁷⁷ Attempts to develop analogues with fewer central side effects have been limited by lack of efficacy and liver toxicity.⁷⁸ Nevertheless, when tolerated, baclofen is an option for patients whose symptoms persist despite PPI therapy.^{79,80}

Adjunct Medications

Antacids are basic aluminium, calcium, or magnesium compounds primarily used to manage intermittent esophageal symptoms, particularly heartburn. Their main advantage is rapid relief of symptoms. Antacids do not provide prolonged symptom relief, heal erosive esophagitis, or prevent GERD complications.^{81,82} Alginates can create a physical barrier against reflux by forming a raft and increasing the viscosity of gastric content. Alginates are particularly useful in neutralizing the acid pocket, which consists of a layer of supernatant acid in the proximal stomach on top of an ingested meal.⁸³ When used in combination with an antacid, alginates are better in reducing heartburn and AET than antacids alone,^{83–85} and may augment symptom control over use of PPIs alone.⁸⁶ Antacid-lidocaine combinations are sometimes given to patients with acute retrosternal discomfort, but symptom response varies⁸⁷; and symptom improvement is unreliable in excluding a coronary mechanism for symptoms.⁸⁸

Sucralfate, a complex of sucrose sulphate and aluminium hydroxide, binds to denuded mucosa in the foregut. It is used to treat patients with erosive gastroduodenal disease, particularly stress ulcers. Sucralfate has higher levels of efficacy than placebo in patients with erosive esophagitis, but its benefit has not been established in patients with nonerosive reflux disease.⁸⁹ Also, sucralfate must be taken as often as 4 times per day. The availability of effective, alternate medications (PPIs, H2RAs), limits the routine use of sucralfate to pregnant women or patients with erosive disease that does not respond to acid suppression.

Prokinetic agents (metoclopramide, domperidone, mosapride, and itopride) are sometimes considered for patients with symptoms of GERD to increase LES basal tone, increase esophageal clearance of refluxate, and accelerate gastric emptying. However, a meta-analysis of randomized studies found only modest reductions in symptom scores when prokinetics were added to PPI therapy. The combination did not increase healing of erosive esophagitis or improve esophageal motor performance, but did increase risk of adverse events.⁷⁷ It is likely that these agents are beneficial primarily in GERD with delayed gastric emptying documented by objective tests.

Invasive Management Including Antireflux Surgery

Antireflux Surgery

After peaking in 2009, use of antireflux surgery (ARS) decreased to levels a decade ago (0.05% of patients with

GERD), indicating reduced enthusiasm among referring physicians and patients alike.⁹⁰ For the average patient, ARS is pursued in the following 3 settings: as an option for long-term management of GERD over medical therapy, for persistent proven GERD symptoms or esophageal mucosal damage despite maximal medical therapy, and when there is significant structural disruption at the EGJ (eg, large hiatus hernia). Outcomes of ARS are comparable to those of long-term PPI therapy in randomized clinical trials,^{91–93} provided GERD is defined in terms of abnormal esophageal reflux burden.⁹⁴ In these patients, symptom response to PPI, limited esophagitis on endoscopy, and barium esophagram showing hiatus hernia are unreliable predictors of abnormal reflux burden,^{94,95} and cannot be substituted for ambulatory reflux monitoring, typically performed off antisecretory therapy.⁶

ARS reliably reduces symptoms in patients with proven GERD; as many as 90% of patients are symptom free at 10 years of follow-up,⁹⁶ and 60% remain off PPIs at 17 years of follow-up.⁹⁷ Other investigators report as many as 60% to 80% resume antisecretory therapy over long-term follow-up, although stopping medications may not necessarily worsen symptoms.⁹⁸ Good evidence for GERD (eg, abnormal AET on pH monitoring, absence of esophageal outflow obstruction on manometry), response to antisecretory therapy, and typical reflux symptoms (rather than atypical symptoms) predict symptom improvement following surgical intervention.⁹⁹ The presence of a hiatus hernia also predicts better satisfaction from ARS.¹⁰⁰ In patients with proven GERD, persistence of heartburn and reflux symptoms is lower with ARS than with medical therapy in the short term (relative risk 0.45) as well as the long term (relative risk 0.56).¹⁰¹ However, dysphagia occurs in higher proportions of patients who undergo ARS (10.2%–12.9%) compared with those who receive medical therapy (1.9%–3.6%).¹⁰¹ Reductions in atypical symptoms are less predictable following ARS, especially when response to antisecretory therapy has not been established.¹⁰²

ARS can be associated with troublesome abdominal bloating, related to inability to vent swallowed air, and to increased perception of gastric distension.¹⁰³ Early dysphagia is common during the first 4 to 6 weeks following ARS; persisting dysphagia beyond 12 weeks can result from morphological EGJ abnormalities or esophageal motor dysfunction.¹⁰⁴ Tailoring fundoplication to esophageal peristaltic function can reduce likelihood of late postoperative dysphagia, when complete 360-degree fundoplication is reserved for patients with intact peristaltic performance, and partial fundoplication (Toupet or Dor) is performed in those with suboptimal esophageal peristaltic function.^{104,105} Repeat surgery is reported for recurrent GERD symptoms or dysphagia in 16% of patients.⁹⁷ When fundoplication fails, reasons frequently include use for the wrong indication, incomplete preoperative evaluation, and improper surgical technique.¹⁰⁶

Bariatric Surgery

Roux-en-Y gastric bypass is effective in reducing reflux in morbidly obese patients; it also decreases esophageal

reflux burden and GERD symptoms in addition to reducing weight and obesity-related comorbidities.¹⁰⁷ This option has been used both as an initial surgical approach and following failed fundoplication.¹⁰⁸ Roux-en-Y bypass surgery is generally safer, in terms of lower in-hospital complications, than laparoscopic fundoplication in morbidly obese patients, whereas hospital costs, length of stay, and mortality are comparable.¹⁰⁹ In contrast, the gastric-sleeve procedure augments reflux mechanisms and can consistently worsen symptoms of GERD.

Magnetic Sphincter Augmentation

A bracelet of titanium-encased magnets can be surgically implanted at the EGJ to augment the LES in patients with symptomatic GERD. The magnets separate to allow sphincter opening for food passage, but prevent retrograde movement of gastric content.¹¹⁰ The bracelet can be sized to fit varying EGJ circumference, and can be implanted laparoscopically with minimal intraoperative complications. Magnetic sphincter augmentation (MSA) was initially studied in patients with proven GERD in the absence of hiatus hernia larger than 3 cm, esophageal dysmotility, or GERD complications. MSA normalized distal AET in 58% of patients at 1 year, and reduced PPI usage by at least half in 93% of the patients.¹¹² Dysphagia was initially reported by 68% of patients, but the frequency decreased to 4% at 3 years; dysphagia was the primary reason for removal of the device in 4 patients in the first 3 months.¹¹¹

Intermediate and long-term outcomes are now available for up to 5 years. When outcomes of ARS were compared with those of MSA in a retrospective study, GERD-related quality of life and rates of PPI use were similar at 1 year.¹¹² In the original cohort of 100 subjects, 89% of the patients reported heartburn at baseline which decreased to 12% at 5 years; regurgitation decreased from 57% of patients to 1%.¹¹³ Daily use of PPIs decreased from 100% of the patients at baseline to 15.3% at 5 years, and double-dose PPI use decreased from 36.0% to 2.4%.¹¹³ Device removal was required in 3.4% to 7.0% of patients, due to dysphagia, continued reflux, or chest pain.^{113,114} Device erosion rates are reported to be below 1%. Severe gas bloat symptoms and inability to belch were less troublesome following MSA compared with traditional ARS.¹¹² In a meta-analysis of case-control studies comparing MSA with ARS, MSA was superior in preserving ability to belch and vomit, with comparable discontinuation of PPI use and improvement in quality of life.¹¹⁵

Therefore, MSA may be a viable alternative to ARS for patients with well-documented reflux disease, particularly patients with regurgitation, in the absence of significant structural disruption at the EGJ, or esophageal body motor dysfunction. However, the long-term consequences of having an implanted titanium bracelet need to be better understood.

Endoscopic Therapy

Over the past 20 years, there have been studies of several forms of endoscopic intervention for management

of GERD, but most have been withdrawn for either lack of efficacy or undesirable complications. Only 2 endoscopic interventions are currently available: radiofrequency application (RFA) at the EGJ, and transoral incisionless fundoplication (TIF). In studies evaluating these endoscopic interventions, patients with significant structural EGJ disruption (eg, hiatus hernia larger than 2 cm), significant esophagitis (Los Angeles Classification of GERD grade C or D), and GERD complications (BE, peptic stricture) were excluded.

Endoscopic RFA to the EGJ was introduced 15 years ago, with the expectation that hypertrophy and possibly scarring of the LES would increase LES pressure and reduce the frequency of TLESRs. Although RFA is safe, early comparisons to sham procedures indicated that improvement was limited to subjective clinical parameters.¹¹⁶⁻¹¹⁸ A meta-analysis of randomized controlled trials did not report normalization of AET, discontinuation of PPIs, or improved quality of life following RFA.¹¹⁸ However, another meta-analysis that included both randomized controlled trials and nonrandomized longitudinal cohort studies found improvements in health-related quality of life and reductions in esophageal acid burden and PPI use.¹¹⁷ Neither meta-analysis reported increase in LES pressures.

Endoscopic suturing using prototype devices can create a structural barrier between the stomach and the esophagus. T-fasteners are used to create an endoscopic fundoplication in TIF. In a multicenter study that compared TIF to a sham procedure and PPI therapy, esophageal pH decreased and regurgitation was better resolved 6 months after TIF, although TIF did not reduce GERD symptom scores.¹¹⁹ In a randomized study that compared TIF with PPI therapy, after 12 months of follow-up, patients who received TIF had a nonsignificant reduction in esophageal AET, and 61% of patients resumed PPI therapy, with visible deterioration of the fundoplication over time.¹²⁰ A recent meta-analysis demonstrated that TIF reduced acid exposure and acid reflux episodes to a limited extent. However, most patients resumed PPI use over time.¹²¹

Although more studies have been evaluating the efficacy of ARS, and recent data from MSA studies are encouraging, some patients are interested in nonmedical and nonsurgical therapeutics. These include patients with allergies to antisecretory agents, patients not interested in medical or surgical therapy, patients who are poorly compliant, and patients concerned about long-term PPI therapy. RFA and TIF could be options for these types of patients with well-characterized GERD, in special circumstances.

PPI Nonresponders

As many as 40% of patients with heartburn have either an incomplete or complete lack of response to once-daily PPIs.¹²² The proportion of patients with persistent troublesome heartburn despite once-daily PPI use was 32% in randomized trials and 17% in nonrandomized trials, respectively; the proportion of patients with persistent regurgitation was 28% in randomized and nonrandomized trials.¹²³ As many as 54% of patients with GERD might

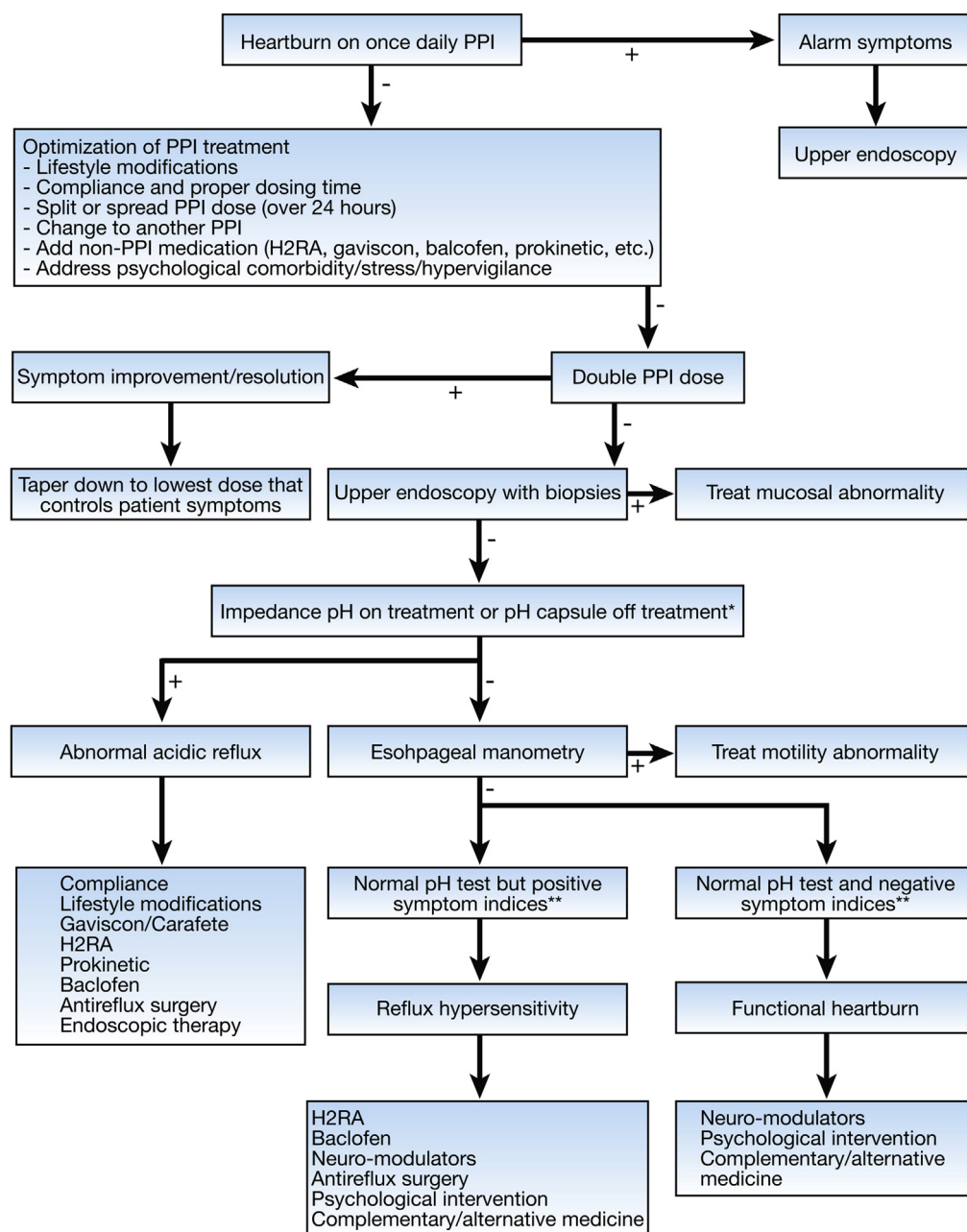


Figure 1. Algorithm for evaluation and management of patients who do not respond to PPI therapy. Initially, once-daily PPI therapy is optimized, with consideration of twice-daily PPI therapy. Objective testing with endoscopy and ambulatory reflux monitoring can identify patients with proven GERD (which can improve with escalation of antireflux therapy), from functional and non-GERD syndromes that do not improve with acid suppression. When invasive management is indicated, all therapeutic options should be considered for patients with well-characterized GERD, and specifically selected for each individual based on the circumstances. Some patients have overlap syndromes, with GERD and functional esophageal disorders. *In patients with proven GERD (abnormal pH test or erosive esophagitis), pH-impedance testing is performed on treatment; in all others (unproven GERD), pH or pH-impedance testing off treatment (prolonged wireless pH monitoring may have advantages). **With either acidic or nonacidic reflux.

not take their PPIs optimally, which reduces efficacy.¹²⁴ Increasing compliance and ensuring proper PPI dosing are important strategies for reducing overuse of double doses of PPIs⁵ (Figure 1).

Optimization

Perceived severity of GERD symptoms; number of pills consumed per day; patient age, sex, and social status; and other factors compromise compliance to PPI therapy.¹²⁵ One study found 45% of patients to be noncompliant 4 weeks after receiving their first prescription for PPIs.¹²⁶ Additionally, 37% of patients took their PPI for 12 days or fewer each month. Another study found fewer than 50% of

patients to be compliant with once-daily PPI use by 3 months after receiving the drug for the first time.¹²⁷

Although taking PPIs 30 to 45 minutes before a meal has been reported to improve control of intragastric pH,¹²⁸ patients are frequently uninformed about correct PPI dosing. Most patients (71%) take the PPI appropriately before meals when the drug is prescribed by a gastroenterologist, but only 39% do so when they purchase it over-the-counter.¹²⁹ Another study found that none of the patients with heartburn who failed to respond to once-daily PPI therapy was taking the medication correctly.¹²⁴ Optimization of PPI dosing is an integral part of managing patients who report partial or complete lack of response to standard-dose PPI therapy¹³⁰; increasing compliance

is necessary to obtain the maximum benefits from these drugs (Figure 1).

Splitting or spreading the standard dose of a PPI has been shown to increase control of intragastric pH. For example, esomeprazole administered in a split dose (20 mg before breakfast and dinner) resulted in better control of intragastric pH compared with a standard 40-mg dose before breakfast. Intragastric pH >4 was achieved by 76.5% of patients taking a split dose vs 68.8% taking a single dose; median intragastric pH was 4.9 in patients taking the split dose vs 4.8 in those taking a single dose.¹²⁸ Most importantly, the split dose provided better control of nighttime intragastric pH. Patients taking 10 mg rabeprazole 4 times daily had a higher median intragastric pH (6.6) than patients taking 20 mg twice daily (pH 5.7) or 40 mg once daily (4.8).¹³⁵ However, clinical correlation between intragastric pH and symptom reduction is not available, and increasing frequency of PPI administration may reduce overall compliance with therapy.

Another management strategy involves switching to an alternate PPI brand, despite negligible objective differences in PPI efficacy.³⁸ In a randomized trial of patients with heartburn who did not respond to once-daily lansoprazole (30 mg), patients switched to single-dose esomeprazole (40 mg) had similar proportions of heartburn-free days over an 8-week period as patients receiving twice-daily lansoprazole (30 mg) (54.4% vs 57.5%, respectively).¹³⁶ In a separate study, 88% of patients receiving twice-daily PPIs (any formulation) could successfully step down to once-daily dexlansoprazole (30 mg).¹³⁷

Because a growing number of patients are concerned about long-term use of PPIs, physicians can consider adding an alternate antireflux medication to a once-daily PPI. Adding H₂ blockers, sucralfate, antacids, prokinetic agents, and baclofen to once-daily PPIs have been proposed to control symptoms, although these have not necessarily been studied.^{11,74,138-140} Psychologic comorbidities, stress, and hypervigilance all exacerbate symptoms, increase health care use, and affect response to PPI treatment.¹⁴¹⁻¹⁴³ Early intervention should therefore be considered for patients reporting partial or complete lack of response to PPI treatment. Evaluation by a psychologist or psychiatrist, preferably with expertise in gastrointestinal disorders, could prevent the need for escalating PPI doses.¹⁴⁴

When symptoms persist despite optimization of once-daily PPI therapy, a common strategy is to increase the dosage to twice per day, endorsed by most gastroenterology societies.^{5,41} There are benefits to doubling the dose: healing of erosive esophagitis can increase by 6% to 19% and heartburn relief can increase by 22% to 26%.¹³¹⁻¹³⁴ A Cochrane review associated doubling the PPI dose with greater rates of healing in patients with erosive esophagitis, but with a number needed to treat of 25.⁴⁹ Patients prescribed a double dose should take the first dose before breakfast and the second dose before dinner.

Refractory GERD vs Refractory Heartburn

Refractory GERD and refractory heartburn have been used interchangeably for lack of response to twice-daily PPI therapy. However, the terms represent different clinical

scenarios, although not necessarily different patient groups. Refractory GERD is defined as symptoms caused by the reflux of gastric contents that do not respond to a stable double dose of a PPI over a 12-week treatment period.¹⁴⁵ The emphasis of this definition is that symptoms (heartburn and regurgitation) are clearly related to gastroesophageal reflux. However, refractory GERD could include patients with reflux hypersensitivity, a functional esophageal disorder.⁹ For patients with refractory GERD, lifestyle modification, compliance, proper PPI dose, psychological comorbidity, and overlap with functional esophageal or other functional bowel disorders should be sought out.^{9,146}

Refractory heartburn, on the other hand, can be caused by various mechanisms, either exclusively without GERD or in addition to GERD. Refractory heartburn is defined as heartburn that does not respond to a stable double-dose PPI over a 12-week treatment period.¹⁴⁷⁻¹⁴⁹ Possible mechanisms include noncompliance, improper dose, reduced bioavailability, rapid PPI metabolism, eosinophilic esophagitis, esophageal dysmotility (such as achalasia), skin disorders that involve the esophagus, delayed gastric emptying, concomitant functional bowel disorders, and psychological comorbidities.^{122,145,147} Refractory heartburn can therefore occur in patients with the various GERD phenotypes (BE, NERD, or erosive esophagitis), but most importantly, functional esophageal disorders could participate in symptom generation.⁹

Functional Esophageal Disorders

Management of refractory heartburn requires understanding of the Rome IV definitions of functional heartburn and reflux hypersensitivity.⁹ Functional heartburn consists of burning retrosternal discomfort or pain, with lack of symptom relief despite optimal antisecretory therapy. Patients with reflux hypersensitivity have similar symptoms, but there is evidence that symptoms are triggered by reflux episodes on ambulatory reflux monitoring, in the setting of physiologic AETs.⁹ In making a diagnosis of these functional esophageal disorders, pathologic GERD, eosinophilic esophagitis, major esophageal motor disorders, and structural abnormalities need to be excluded. Both functional heartburn and reflux hypersensitivity can overlap with established GERD.

Based on ambulatory pH or pH-impedance monitoring, as many as 21% to 24% of treatment-naïve patients with heartburn have functional heartburn, and another 14% to 36% have reflux hypersensitivity.^{150,151} Of patients who do not respond to twice-daily PPI therapy, 29% to 39% have functional heartburn and 28% to 36% have reflux hypersensitivity.^{10,152,153} Functional heartburn and reflux hypersensitivity are therefore thought to account for refractory heartburn in most patients who have not responded to twice-daily PPI therapy.^{5,9} Identifying these disorders in patients with refractory heartburn is pivotal in developing an effective therapeutic approach.

Management of Refractory Heartburn

Management recommendations for patients with refractory heartburn (Figure 1) incorporate elements within

the Rome IV management algorithms.⁹ Evaluation typically starts with an upper endoscopy, with biopsy to exclude eosinophilic esophagitis.^{5,9,122} Although it is unlikely that endoscopy will find features that affect management,¹⁵⁴ eosinophilic and lymphocytic esophagitis, achalasia, skin disorders that involve the esophagus, and other uncommon disorders need to be excluded.

If endoscopy with biopsy is negative, patients undergo ambulatory reflux monitoring. Although either pH or pH-impedance monitoring off therapy is appropriate for patients with no prior evidence of GERD (unproven GERD), prolonged pH monitoring with a wireless pH capsule, when available, may provide added value.^{5,6,9,155,156} In contrast, patients with proven GERD (abnormal pH test and/or erosive esophagitis on upper endoscopy) should undergo pH-impedance monitoring on PPI therapy.^{5,9,155,156}

Normal AET on ambulatory reflux monitoring should prompt esophageal manometry. If esophageal manometry does not detect a major motor disorder, symptom-reflux association on reflux monitoring can further characterize the heartburn presentation, primarily in separating reflux hypersensitivity (positive symptom indices for both acidic and weakly acidic reflux) from functional heartburn (negative symptom indices). Esophageal hypersensitivity is the mechanism underlying reflux hypersensitivity and functional heartburn, and may account for most patients with heartburn who do not respond to twice-daily PPIs.^{46,156–158} Patients with proven GERD who have not responded to twice-daily PPI therapy might also have an overlapping functional esophageal disorder, if they have normal findings on endoscopy and normal AET on ambulatory reflux monitoring.⁹

Treating Functional Esophageal Disorders

All patients with functional esophageal disorders should be reassured about the benign nature of their symptoms. Most

patients require medical intervention, and some may require more comprehensive management from psychologists or psychiatrists, alternative/complementary medicine therapists, acupuncturists, or other experts in functional medicine.

Neuromodulators are the mainstay of the management of functional esophageal disorders. Neuromodulators alter neuronal function without acting as neurotransmitters, and confer their effect on esophageal pain by modulating central hyperalgesia, and to some degree, peripheral hyperalgesia.¹⁵⁹ Tricyclic antidepressants, trazodone, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors have been found to be effective in treatment of functional esophageal disorders, primarily noncardiac chest pain (Table 3).^{160–174} Although the use of antidepressants is attractive, few studies have demonstrated their efficacy in patients with functional heartburn. In a randomized, double-blind, placebo-controlled trial of patients with functional heartburn who did not respond to once-daily PPIs, fluoxetine (20 mg) as add-on therapy was more effective compared with a double dose of a PPI or placebo.¹⁷¹ In a separate study, patients with reflux hypersensitivity and functional heartburn given a fixed, once-daily dose of imipramine (25 mg) had similar responses in symptoms as patients given placebo.¹⁶³ However, tricyclic antidepressants should not be administered in a fixed dose; the dose should be carefully increased, in small increments, on a case-by-case basis, depending on symptomatic response.¹⁷⁵

Among other options, H2RAs can modulate esophageal acid sensitivity in patients with functional heartburn; a single 150-mg dose of ranitidine significantly reduced esophageal sensitivity to acid infusion compared with placebo in functional heartburn defined according to Rome II criteria.¹⁷⁶ Tegaserod, a partial 5-hydroxytryptamine 4 antagonist, improved esophageal chemo- and mechano-receptor sensitivity, and reduced

Table 3. Neuromodulators Studied in Randomized-Controlled Trials of Patients With Functional or Nonfunctional Esophageal Disorders

Name	Class of drugs	Disorder	Dose	Response rate	Side effects
Imipramine ¹⁶¹	TCAs	NCCP	50 mg/d	52%	QT prolongation
Imipramine ¹⁶²	TCAs	NCCP	50 mg/d	Significant	Dry mouth, dizziness
Imipramine ¹⁶³	TCAs	FH, RH	25 mg/d	37.2%	Constipation
Amitriptyline ^{164,165}	TCAs	NCCP, globus	10,25 mg/d	52%, significant	Excessive sleeping, dizziness
Sertraline ¹⁶⁶	SSRIs	NCCP	50–200 mg/d	57%	Nausea, restlessness
Sertraline ¹⁶⁷	SSRIs	NCCP	50–200 mg/d	Modest	Dry mouth, diarrhea
Paroxetine ¹⁶⁸	SSRIs	NCCP	10–50 mg/d	Modest	Fatigue, dizziness
Paroxetine ¹⁶⁹	SSRIs	NCCP	10–50 mg/d	21.7%	None
Citalopram ¹⁷⁰	SSRIs	RH	20 mg/d	Significant	None
Fluoxetine ¹⁷¹	SSRIs	FH/RH	20 mg/d	Significant	Headache, dry mouth
Trazodone ¹⁶⁰	SRI	Dysmotility	100–150 mg/d	29%–41%	Dry mouth, dizziness
Venlafaxine ¹⁷²	SNRIs	NCCP	75 mg/d	52%	Sleep disturbances
Ranitidine ¹⁷⁶	H2RAs	FH	300 mg/d	Significant	None
Theophylline ¹⁷³	Adenosine antagonists	NCCP	200 mg twice per d	58%	Nausea, insomnia, tremor
Gabapentin ¹⁷⁴	GABA analog	Globus	300 mg 3 times per d	66%	None

FH, functional heartburn; GABA, gamma-aminobutyric acid; NCCP, noncardiac chest pain; RH, reflux hypersensitivity; SNRIs, serotonin-norepinephrine reuptake inhibitors; SRIs, serotonin reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

heartburn symptoms compared with placebo in patients with functional heartburn.¹⁷⁷ However, tegaserod is no longer available for clinical use. Melatonin (6 mg, once daily for 3 months) significantly reduced heartburn symptoms compared with nortriptyline (25 mg) or placebo in a randomized trial.¹⁷⁸ In an open-label study, 7 weekly sessions of hypnotherapy significantly decreased visceral anxiety and symptom severity in patients with functional heartburn.¹⁷⁹

Because symptoms are induced by reflux episodes in patients with reflux hypersensitivity, medical, endoscopic, and surgical antireflux therapies are often initially considered. Little is known about the effects of diet and lifestyle modifications. As in patients with functional heartburn, H2RAs could reduce esophageal chemoreceptor sensitivity to acid in patients with reflux hypersensitivity,¹⁸⁰ although there have been no specific studies of these effects. When patients with Rome II-defined functional heartburn were treated with PPIs twice daily, only those with positive symptom index (the reflux hypersensitivity group) responded to treatment, indicating a role for minimization of esophageal acid exposure. It is unclear if twice-daily PPI therapy is a plateau dose, as for patients with GERD, or if further acid suppression with higher doses could provide better therapeutic benefit. ARS has been successful in carefully selected patients with reflux hypersensitivity diagnosed using pH-impedance monitoring^{10,181,182}; it reduced acidic, weakly acidic, and liquid and mixed reflux episodes following fundoplication.¹⁸² Regardless, very few studies have assessed the value of invasive options (ARS, endoscopic therapies) in patients with reflux hypersensitivity; more data are needed.

As for patients with functional heartburn, patients with reflux hypersensitivity may benefit from neuromodulators. There have been few studies of specific treatments for these patients. In a randomized, placebo-controlled trial, patients with reflux hypersensitivity given daily citalopram (20 mg) for 6 months had significant reductions in symptoms compared with patients given placebo.¹⁸³

Alternative medicine modalities, such as acupuncture, have been reported to reduce heartburn in patients who did not respond to once-daily PPI therapy. These studies likely included patients with both functional heartburn and reflux hypersensitivity.¹⁸⁴ Diaphragmatic breathing may also complement management of GERD.¹⁸⁵

Future Directions

Drug development in GERD has considerably decreased over the past decade, primarily because most PPIs have become generic and are available over-the-counter.¹⁸⁶ In contrast, there has been growing interest in nonmedical therapeutic strategies, especially for patients who are not interested in, allergic to, noncompliant with, or concerned about long-term PPI treatment.¹⁸⁷

Potassium-competitive acid blockers (P-CABs) inhibit the proton pump in a K^+ competitive but reversible mechanism. P-CABs demonstrate significant early-onset inhibition of acid secretion in response to a rapid rise in peak plasma concentration.¹⁸⁸ Vonoprazan was the first P-CAB to

be used clinically,¹⁸⁹ but it is not available in the United States. A 20-mg dose healed 99% of patients with erosive esophagitis in 8 weeks, compared with lansoprazole (30 mg), which healed 95.5% of patients¹⁹⁰; healing was maintained for 52 weeks in 90% of patients. Although this drug has an excellent safety profile, increases in gastrin (up to threefold to fourfold the upper limit of normal) were reported in patients who received the 20-mg dose; the clinical significance of this increase is unclear. It is also unclear whether P-CABs are more effective in reducing symptoms than other existing acid suppressants.¹⁹¹

IW-3718 is an investigational gastric retentive formulation of a bile acid sequestrant. It has been evaluated as an adjunct therapy for patients with a suboptimal response to a standard dose of PPIs. In a phase 2A randomized, double-blind placebo-controlled trial, the percentage of heartburn-free days increased by 30.3% in patients given IW-3718, and by 34.6% in patients with bile reflux, compared with 24.7% and 23.6%, respectively, in patients given placebo.¹⁹²

MUSE (Medigus, Omer, Israel) is an endoscopic stapling device for anterior fundoplication. It uses a modified endoscope that incorporates a miniature camera, an ultrasound probe, and a stapler at the tip.¹⁹³ Several short-term studies have shown the efficacy of this technique in reducing symptoms and improving health-related quality of life. The treatment reduces PPI use and esophageal acid exposure.¹⁹⁴ An injectable bulking agent (Impleo Medical, St Paul, MN) delivered into the submucosal tissue of the LES during endoscopy has been assessed in patients with GERD. The injections create tissue bulges that mechanically impede gastroesophageal reflux. However, there are few data to demonstrate efficacy.¹⁹⁵

Electrical stimulation has been shown to increase LES resting pressure in animal models.^{196–198} In several studies, short-term electrical stimulation of the LES increased resting pressure, reduced esophageal acid exposure, improved GERD health-related quality of life, and reduced PPI use without affecting the amplitude of esophageal peristalsis or LES relaxation.^{199,200} A long-term follow-up analysis (up to 2 years) of patients who received the device revealed durability of these effects.²⁰¹

Other therapeutic strategies under development for GERD, such as TLESR reducers or combinations of PPIs and prokinetic agents, have met obstacles. Mucosal protectants and esophageal pain modulators have potential to provide novel approaches to treating GERD. Specifically, pain modulators might have potential in treating patients with NERD or NERD overlapping with a functional esophageal disorder.

Conclusions

Current strategies for management of GERD are based on several decades of pharmaceutical and non-pharmacologic therapeutic development that have considered the risks, albeit limited, of chronic acid suppression. There is growing recognition that functional esophageal disorders (functional heartburn and reflux hypersensitivity) are the leading mechanisms for persistent heartburn. The basic tenets of GERD management today are as follows:

management with a PPI only when necessary, at the lowest dose that controls symptoms; optimization of therapy when symptoms persist despite once-daily PPI use in patients with proven GERD; use of upper endoscopy and esophageal function tests to determine mechanisms of symptom generation (proven GERD vs non-GERD mechanisms) when symptoms persist despite optimal PPI therapy; and consideration of other medical therapies, antireflux surgery, or endoscopic interventions, for patients unable to tolerate or not interested in acid suppression. Neuromodulators are the mainstay of management of functional esophageal disorders.

References

1. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014;63:871–880.
2. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. *Am J Gastroenterol* 2006;101:2128–2138.
3. Fass R, Ofman JJ, Gralnek IM, et al. Clinical and economic assessment of the omeprazole test in patients with symptoms suggestive of gastroesophageal reflux disease. *Arch Intern Med* 1999;159:2161–2168.
4. Fass R, Ofman JJ, Sampliner RE, et al. The omeprazole test is as sensitive as 24-h oesophageal pH monitoring in diagnosing gastro-oesophageal reflux disease in symptomatic patients with erosive oesophagitis. *Aliment Pharmacol Ther* 2000;14:389–396.
5. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308–328; quiz 329.
6. Roman S, Gyawali CP, Savarino E, et al. Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. *Neurogastroenterol Motil* 2017;29:1–15.
7. Patel A, Sayuk GS, Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2015;13:884–891.
8. Patel A, Sayuk GS, Kushnir VM, et al. GERD phenotypes from pH-impedance monitoring predict symptomatic outcomes on prospective evaluation. *Neurogastroenterol Motil* 2016;28:513–521.
9. Aziz Q, Fass R, Gyawali CP, et al. Functional esophageal disorders [published online ahead of print February 15, 2016]. *Gastroenterology* <https://doi.org/10.1053/j.gastro.2016.02.012>.
10. Patel A, Sayuk GS, Gyawali CP. Prevalence, characteristics, and treatment outcomes of reflux hypersensitivity detected on pH-impedance monitoring. *Neurogastroenterol Motil* 2016;28:1382–1390.
11. Fass R. Alternative therapeutic approaches to chronic proton pump inhibitor treatment. *Clin Gastroenterol Hepatol* 2012;10:338–345; quiz e39–e40.
12. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med* 2006;166:965–971.
13. El-Serag H. The association between obesity and GERD: a review of the epidemiological evidence. *Dig Dis Sci* 2008;53:2307–2312.
14. El-Serag HB, Graham DY, Satia JA, et al. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. *Am J Gastroenterol* 2005;100:1243–1250.
15. Ayazi S, Hagen JA, Chan LS, et al. Obesity and gastro-esophageal reflux: quantifying the association between body mass index, esophageal acid exposure, and lower esophageal sphincter status in a large series of patients with reflux symptoms. *J Gastrointest Surg* 2009;13:1440–1447.
16. Jacobson BC, Somers SC, Fuchs CS, et al. Body-mass index and symptoms of gastroesophageal reflux in women. *N Engl J Med* 2006;354:2340–2348.
17. Mathus-Vliegen EM. [Nutrition and health—ideal body weight for the obese unrealistic; health benefit by moderate sustained weight loss]. *Ned Tijdschr Geneeskde* 2003;147:1168–1172. Dutch.
18. Mathus-Vliegen LM, Tytgat GN. Twenty-four-hour pH measurements in morbid obesity: effects of massive overweight, weight loss and gastric distension. *Eur J Gastroenterol Hepatol* 1996;8:635–640.
19. Fraser-Moodie CA, Norton B, Gornall C, et al. Weight loss has an independent beneficial effect on symptoms of gastro-oesophageal reflux in patients who are overweight. *Scand J Gastroenterol* 1999;34:337–340.
20. Park SK, Lee T, Yang HJ, et al. Weight loss and waist reduction is associated with improvement in gastro-esophageal disease reflux symptoms: A longitudinal study of 15 295 subjects undergoing health checkups. *Neurogastroenterol Motil* 2017;29(5).
21. Shaker R, Castell DO, Schoenfeld PS, et al. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup survey conducted on behalf of the American Gastroenterological Association. *Am J Gastroenterol* 2003;98:1487–1493.
22. Katz LC, Just R, Castell DO. Body position affects recumbent postprandial reflux. *J Clin Gastroenterol* 1994;18:280–283.
23. Khoury RM, Camacho-Lobato L, Katz PO, et al. Influence of spontaneous sleep positions on nighttime recumbent reflux in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 1999;94:2069–2073.
24. van Herwaarden MA, Katzka DA, Smout AJ, et al. Effect of different recumbent positions on postprandial gastroesophageal reflux in normal subjects. *Am J Gastroenterol* 2000;95:2731–2736.
25. Fujiwara Y, Arakawa T, Fass R. Gastroesophageal reflux disease and sleep. *Gastroenterol Clin North Am* 2013;42:57–70.
26. Orr WC, Harnish MJ. Sleep-related gastro-oesophageal reflux: provocation with a late evening meal and treatment with acid suppression. *Aliment Pharmacol Ther* 1998;12:1033–1038.
27. Watanabe Y, Fujiwara Y, Shiba M, et al. Cigarette smoking and alcohol consumption associated with gastro-oesophageal reflux disease in Japanese men. *Scand J Gastroenterol* 2003;38:807–811.

28. Nilsson M, Johnsen R, Ye W, et al. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. *Gut* 2004;53:1730–1735.
29. Schindlbeck NE, Heinrich C, Dendorfer A, et al. Influence of smoking and esophageal intubation on esophageal pH-metry. *Gastroenterology* 1987;92:1994–1997.
30. Waring JP, Eastwood TF, Austin JM, et al. The immediate effects of cessation of cigarette smoking on gastroesophageal reflux. *Am J Gastroenterol* 1989;84:1076–1078.
31. Rubinstein E, Hauge C, Sommer P, et al. Oesophageal and gastric potential difference and pH in healthy volunteers following intake of coca-cola, red wine, and alcohol. *Pharmacol Toxicol* 1993;72:61–65.
32. Grande L, Manterola C, Ros E, et al. Effects of red wine on 24-hour esophageal pH and pressures in healthy volunteers. *Dig Dis Sci* 1997;42:1189–1193.
33. Grande L, Monforte R, Ros E, et al. High amplitude contractions in the middle third of the oesophagus: a manometric marker of chronic alcoholism? *Gut* 1996;38:655–662.
34. Shaheen NJ, Falk GW, Iyer PG, et al. ACG clinical guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol* 2016;111:30–50; quiz 51.
35. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. *JAMA* 2013;310:627–636.
36. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology* 2000;118:S9–S31.
37. Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology* 2001;120:1599–1606.
38. Gralnek IM, Dulai GS, Fennerty MB, et al. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. *Clin Gastroenterol Hepatol* 2006;4:1452–1458.
39. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology* 2017;152:706–715.
40. Yadlapati R, Kahrilas PJ. When is proton pump inhibitor use appropriate? *BMC Med* 2017;15:36.
41. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology* 2008;135:1383–1391, 1391.e1–e5.
42. Numans ME, Lau J, de Wit NJ, et al. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. *Ann Intern Med* 2004;140:518–527.
43. Weijenborg PW, Cremonini F, Smout AJ, et al. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. *Neurogastroenterol Motil* 2012;24:747–757, e350.
44. Wang AJ, Wang H, Xu L, et al. Predictors of clinical response of acid suppression in Chinese patients with gastroesophageal reflux disease. *Dig Liver Dis* 2013;45:296–300.
45. de Bortoli N, Martinucci I, Savarino E, et al. Proton pump inhibitor responders who are not confirmed as GERD patients with impedance and pH monitoring: who are they? *Neurogastroenterol Motil* 2014;26:28–35.
46. Slaughter JC, Goutte M, Rymer JA, et al. Caution about overinterpretation of symptom indexes in reflux monitoring for refractory gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2011;9:868–874.
47. Taghavi SA, Ghasedi M, Saberi-Firoozi M, et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. *Gut* 2005;54:1067–1071.
48. Kushnir VM, Sayuk GS, Gyawali CP. Abnormal GERD parameters on ambulatory pH monitoring predict therapeutic success in noncardiac chest pain. *Am J Gastroenterol* 2010;105:1032–1038.
49. Khan M, Santana J, Donnellan C, et al. Medical treatments in the short term management of reflux oesophagitis. *Cochrane Database Syst Rev* 2007;(2) CD003244.
50. Chiba N, De Gara CJ, Wilkinson JM, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology* 1997;112:1798–1810.
51. Sabesin SM, Berlin RG, Humphries TJ, et al. Famotidine relieves symptoms of gastroesophageal reflux disease and heals erosions and ulcerations. Results of a multicenter, placebo-controlled, dose-ranging study. USA Merck Gastroesophageal Reflux Disease Study Group. *Arch Intern Med* 1991;151:2394–2400.
52. Dean BB, Gano AD Jr, Knight K, et al. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004;2:656–664.
53. Johnson DA, Benjamin SB, Vakil NB, et al. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. *Am J Gastroenterol* 2001;96:27–34.
54. Sigterman KE, van Pinxteren B, Bonis PA, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* 2013;(5) CD002095.
55. 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;106:1419–1425; quiz 1426.
56. Kahrilas PJ, Jonsson A, Denison H, et al. Regurgitation is less responsive to acid suppression than heartburn in patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2012;10:612–619.
57. Kahrilas PJ, Hughes N, Howden CW. Response of unexplained chest pain to proton pump inhibitor treatment in patients with and without objective evidence of gastroesophageal reflux disease. *Gut* 2011;60:1473–1478.

58. Cremonini F, Wise J, Moayyedi P, et al. Diagnostic and therapeutic use of proton pump inhibitors in non-cardiac chest pain: a metaanalysis. *Am J Gastroenterol* 2005; 100:1226–1232.
59. Wang WH, Huang JQ, Zheng GF, et al. Is proton pump inhibitor testing an effective approach to diagnose gastroesophageal reflux disease in patients with noncardiac chest pain? A meta-analysis. *Arch Intern Med* 2005;165:1222–1228.
60. Chang AB, Lasserson TJ, Gaffney J, et al. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev* 2011;(1)CD004823.
61. Vaezi MF, Richter JE, Stasney CR, et al. Treatment of chronic posterior laryngitis with esomeprazole. *Laryngoscope* 2006;116:254–260.
62. Hersh MJ, Sayuk GS, Gyawali CP. Long-term therapeutic outcome of patients undergoing ambulatory pH monitoring for chronic unexplained cough. *J Clin Gastroenterol* 2010;44:254–260.
63. Kiljander TO, Harding SM, Field SK, et al. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2006;173:1091–1097.
64. Boghossian TA, Rashid FJ, Thompson W, et al. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. *Cochrane Database Syst Rev* 2017;(3)CD011969.
65. Vasiladis KV, Viazis N, Vlachogiannakos J, et al. Efficacy of three different dosages of esomeprazole in the long-term management of reflux disease: a prospective, randomized study, using the wireless Bravo pH system. *Am J Gastroenterol* 2010;105:308–313.
66. Johnson DA, Katz PO, Armstrong D, et al. The safety of appropriate use of over-the-counter proton pump inhibitors: an evidence-based review and Delphi consensus. *Drugs* 2017;77:547–561.
67. Scarpignato C, Gatta L, Zullo A, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases. A position paper addressing benefits and potential harms of acid suppression. *BMC Med* 2016;14:179.
68. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. *Gastroenterology* 2017; 153:35–48.
69. Kia L, Kahrilas PJ. Therapy: Risks associated with chronic PPI use—signal or noise? *Nat Rev Gastroenterol Hepatol* 2016;13:253–254.
70. Habu Y, Maeda K, Kusuda T, et al. “Proton-pump inhibitor-first” strategy versus “step-up” strategy for the acute treatment of reflux esophagitis: a cost-effectiveness analysis in Japan. *J Gastroenterol* 2005; 40:1029–1035.
71. Inadomi JM, Jamal R, Murata GH, et al. Step-down management of gastroesophageal reflux disease. *Gastroenterology* 2001;121:1095–1100.
72. Zhao F, Wang S, Liu L, et al. Comparative effectiveness of histamine-2 receptor antagonists as short-term therapy for gastro-esophageal reflux disease: a network meta-analysis. *Int J Clin Pharmacol Ther* 2016; 54:761–770.
73. Abdul-Hussein M, Freeman J, Castell D. Concomitant administration of a histamine2 receptor antagonist and proton pump inhibitor enhances gastric acid suppression. *Pharmacotherapy* 2015;35:1124–1129.
74. Mainie I, Tutuian R, Castell DO. Addition of a H2 receptor antagonist to PPI improves acid control and decreases nocturnal acid breakthrough. *J Clin Gastroenterol* 2008; 42:676–679.
75. Fackler WK, Ours TM, Vaezi MF, et al. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. *Gastroenterology* 2002;122:625–632.
76. Vela MF, Tutuian R, Katz PO, et al. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. *Aliment Pharmacol Ther* 2003; 17:243–251.
77. Ren LH, Chen WX, Qian LJ, et al. Addition of prokinetics to PPI therapy in gastroesophageal reflux disease: a meta-analysis. *World J Gastroenterol* 2014; 20:2412–2419.
78. Kahrilas PJ, Boeckxstaens G. Failure of reflux inhibitors in clinical trials: bad drugs or wrong patients? *Gut* 2012; 61:1501–1509.
79. van Herwaarden MA, Samsom M, Rydholm H, et al. The effect of baclofen on gastro-oesophageal reflux, lower oesophageal sphincter function and reflux symptoms in patients with reflux disease. *Aliment Pharmacol Ther* 2002;16:1655–1662.
80. Beaumont H, Boeckxstaens GE. Does the presence of a hiatal hernia affect the efficacy of the reflux inhibitor baclofen during add-on therapy? *Am J Gastroenterol* 2009;104:1764–1771.
81. Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. *Scand J Gastroenterol* 1989;24:401–406.
82. Grove O, Bekker C, Jeppe-Hansen MG, et al. Ranitidine and high-dose antacid in reflux oesophagitis. A randomized, placebo-controlled trial. *Scand J Gastroenterol* 1985;20:457–461.
83. Rohof WO, Bennink RJ, Smout AJ, et al. An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2013;11: 1585–1591; quiz e90.
84. Savarino E, de Bortoli N, Zentilin P, et al. Alginate controls heartburn in patients with erosive and non-erosive reflux disease. *World J Gastroenterol* 2012; 18:4371–4378.
85. Leiman DA, Riff BP, Morgan S, et al. Alginate therapy is effective treatment for gastroesophageal reflux disease symptoms: a systematic review and meta-analysis. *Dis Esophagus* 2017;30:1–8.
86. Manabe N, Haruma K, Ito M, et al. Efficacy of adding sodium alginate to omeprazole in patients with non-erosive reflux disease: a randomized clinical trial. *Dis Esophagus* 2012;25:373–380.
87. Berman DA, Porter RS, Graber M. The GI Cocktail is no more effective than plain liquid antacid: a randomized, double blind clinical trial. *J Emerg Med* 2003; 25:239–244.

88. Chan S, Maurice AP, Davies SR, et al. The use of gastrointestinal cocktail for differentiating gastro-oesophageal reflux disease and acute coronary syndrome in the emergency setting: a systematic review. *Heart Lung Circ* 2014;23:913–923.
89. Simon B, Ravelli GP, Goffin H. Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1996;10:441–446.
90. Khan F, Maradey-Romero C, Ganocy S, et al. Utilisation of surgical fundoplication for patients with gastro-oesophageal reflux disease in the USA has declined rapidly between 2009 and 2013. *Aliment Pharmacol Ther* 2016;43:1124–1131.
91. Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 2011;305:1969–1977.
92. Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. *Gut* 2008;57:1207–1213.
93. Mehta S, Bennett J, Mahon D, et al. Prospective trial of laparoscopic nissen fundoplication versus proton pump inhibitor therapy for gastroesophageal reflux disease: seven-year follow-up. *J Gastrointest Surg* 2006;10:1312–1316; discussion 1316–1317.
94. Bello B, Zoccali M, Gullo R, et al. Gastroesophageal reflux disease and antireflux surgery—what is the proper preoperative work-up? *J Gastrointest Surg* 2013;17:14–20; discussion p 20.
95. Jobe BA, Richter JE, Hoppo T, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. *J Am Coll Surg* 2013;217:586–597.
96. Dallemagne B, Weerts J, Markiewicz S, et al. Clinical results of laparoscopic fundoplication at ten years after surgery. *Surg Endosc* 2006;20:159–165.
97. Oor JE, Roks DJ, Broeders JA, et al. Seventeen-year outcome of a randomized clinical trial comparing laparoscopic and conventional nissen fundoplication: a plea for patient counseling and clarification. *Ann Surg* 2017;266:23–28.
98. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001;285:2331–2338.
99. Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg* 1999;3:292–300.
100. Staehelin A, Zingg U, Devitt PG, et al. Preoperative factors predicting clinical outcome following laparoscopic fundoplication. *World J Surg* 2014;38:1431–1443.
101. Garg SK, Gurusamy KS. Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev* 2015;(11)CD003243.
102. Krill JT, Naik RD, Higginbotham T, et al. Association between response to acid-suppression therapy and efficacy of antireflux surgery in patients with extra-esophageal reflux. *Clin Gastroenterol Hepatol* 2017;15:675–681.
103. Kessing BF, Broeders JA, Vinke N, et al. Gas-related symptoms after antireflux surgery. *Surg Endosc* 2013;27:3739–3747.
104. Shaker A, Stoikes N, Drapekin J, et al. Multiple rapid swallow responses during esophageal high-resolution manometry reflect esophageal body peristaltic reserve. *Am J Gastroenterol* 2013;108:1706–1712.
105. Mello MD, Shriver AR, Li Y, et al. Ineffective esophageal motility phenotypes following fundoplication in gastro-oesophageal reflux disease. *Neurogastroenterol Motil* 2016;28:292–298.
106. Patti MG, Allaix ME, Fisichella PM. Analysis of the causes of failed antireflux surgery and the principles of treatment: a review. *JAMA Surg* 2015;150:585–590.
107. Madalosso CA, Gurski RR, Callegari-Jacques SM, et al. The impact of gastric bypass on gastroesophageal reflux disease in morbidly obese patients. *Ann Surg* 2016;263:110–116.
108. Kim M, Navarro F, Eruchalu CN, et al. Minimally invasive Roux-en-Y gastric bypass for fundoplication failure offers excellent gastroesophageal reflux control. *Am Surg* 2014;80:696–703.
109. Varela JE, Hinojosa MW, Nguyen NT. Laparoscopic fundoplication compared with laparoscopic gastric bypass in morbidly obese patients with gastroesophageal reflux disease. *Surg Obes Relat Dis* 2009;5:139–143.
110. Ganz RA. A modern magnetic implant for gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2017;15:1326–1337.
111. Ganz RA, Peters JH, Horgan S, et al. Esophageal sphincter device for gastroesophageal reflux disease. *N Engl J Med* 2013;368:719–727.
112. Reynolds JL, Zehetner J, Wu P, et al. Laparoscopic magnetic sphincter augmentation vs laparoscopic nissen fundoplication: a matched-pair analysis of 100 patients. *J Am Coll Surg* 2015;221:123–128.
113. Ganz RA, Edmundowicz SA, Taiganides PA, et al. Long-term outcomes of patients receiving a magnetic sphincter augmentation device for gastroesophageal reflux. *Clin Gastroenterol Hepatol* 2016;14:671–677.
114. Lipham JC, Taiganides PA, Louie BE, et al. Safety analysis of first 1000 patients treated with magnetic sphincter augmentation for gastroesophageal reflux disease. *Dis Esophagus* 2015;28:305–311.
115. Skubleny D, Switzer NJ, Dang J, et al. LINX(R) magnetic esophageal sphincter augmentation versus Nissen fundoplication for gastroesophageal reflux disease: a systematic review and meta-analysis. *Surg Endosc* 2017;31:3078–3084.
116. Corley DA, Katz P, Wo JM, et al. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. *Gastroenterology* 2003;125:668–676.
117. Fass R, Cahn F, Scotti DJ, et al. Systematic review and meta-analysis of controlled and prospective cohort

- efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease [published online ahead of print February 23, 2017]. *Surg Endosc* <https://doi.org/10.1007/s00464-017-5431-2>.
118. Lipka S, Kumar A, Richter JE. No evidence for efficacy of radiofrequency ablation for treatment of gastroesophageal reflux disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2015;13:1058–1067.e1.
 119. 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;148:324–333.e5.
 120. Witteman BP, Conchillo JM, Rinsma NF, et al. Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2015;110:531–542.
 121. Huang X, Chen S, Zhao H, et al. Efficacy of transoral incisionless fundoplication (TIF) for the treatment of GERD: a systematic review with meta-analysis. *Surg Endosc* 2017;31:1032–1044.
 122. Hershcovici T, Fass R. Step-by-step management of refractory gastroesophageal reflux disease. *Dis Esophagus* 2013;26:27–36.
 123. El-Serag H, Becher A, Jones R. Systematic review: persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies. *Aliment Pharmacol Ther* 2010;32:720–737.
 124. Gunaratnam NT, Jessup TP, Inadomi J, et al. Sub-optimal proton pump inhibitor dosing is prevalent in patients with poorly controlled gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2006;23:1473–1477.
 125. Fass R, Shapiro M, Dekel R, et al. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease—where next? *Aliment Pharmacol Ther* 2005;22:79–94.
 126. Dickman R, Maradey-Romero C, Gingold-Belfer R, et al. Unmet needs in the treatment of gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2015;21:309–319.
 127. Van Soest EM, Siersema PD, Dieleman JP, et al. Persistence and adherence to proton pump inhibitors in daily clinical practice. *Aliment Pharmacol Ther* 2006;24:377–385.
 128. Wilder-Smith C, Rohss K, Bokelund Singh S, et al. The effects of dose and timing of esomeprazole administration on 24-h, daytime and night-time acid inhibition in healthy volunteers. *Aliment Pharmacol Ther* 2010;32:1249–1256.
 129. Sheikh I, Waghay A, Waghay N, et al. Consumer use of over-the-counter proton pump inhibitors in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 2014;109:789–794.
 130. Sandhu DS, Fass R. Current trends in the management of gastroesophageal reflux disease [published online ahead of print April 24, 2017]. *Gut Liver* <https://doi.org/10.5009/gnl16615>.
 131. Fass R. Persistent heartburn in a patient on proton-pump inhibitor. *Clin Gastroenterol Hepatol* 2008;6:393–400.
 132. Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. *Gastroenterology* 1988;95:903–912.
 133. Fass R, Murthy U, Hayden CW, et al. Omeprazole 40 mg once a day is equally effective as lansoprazole 30 mg twice a day in symptom control of patients with gastro-oesophageal reflux disease (GERD) who are resistant to conventional-dose lansoprazole therapy—a prospective, randomized, multi-centre study. *Aliment Pharmacol Ther* 2000;14:1595–1603.
 134. Kinoshita Y, Hongo M, Japan TSG. Efficacy of twice-daily rabeprazole for reflux esophagitis patients refractory to standard once-daily administration of PPI: the Japan-based TWICE study. *Am J Gastroenterol* 2012;107:522–530.
 135. Sugimoto M, Shirai N, Nishino M, et al. Rabeprazole 10 mg q.d.s. decreases 24-h intragastric acidity significantly more than rabeprazole 20 mg b.d. or 40 mg o.m., overcoming CYP2C19 genotype. *Aliment Pharmacol Ther* 2012;36:627–634.
 136. Fass R, Sontag SJ, Traxler B, et al. Treatment of patients with persistent heartburn symptoms: a double-blind, randomized trial. *Clin Gastroenterol Hepatol* 2006;4:50–56.
 137. Fass R, Inadomi J, Han C, et al. Maintenance of heartburn relief after step-down from twice-daily proton pump inhibitor to once-daily dexlansoprazole modified release. *Clin Gastroenterol Hepatol* 2012;10:247–253.
 138. Reimer C, Lodrup AB, Smith G, et al. Randomised clinical trial: alginate (Gaviscon Advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. *Aliment Pharmacol Ther* 2016;43:899–909.
 139. Lee JY, Kim SK, Cho KB, et al. A double-blind, randomized, multicenter clinical trial investigating the efficacy and safety of esomeprazole single therapy versus mosapride and esomeprazole combined therapy in patients with esophageal reflux disease. *J Neurogastroenterol Motil* 2017;23:218–228.
 140. Vakil NB, Huff FJ, Cundy KC. Randomised clinical trial: arbaclofen placarbil in gastro-oesophageal reflux disease—insights into study design for transient lower sphincter relaxation inhibitors. *Aliment Pharmacol Ther* 2013;38:107–117.
 141. Boltin D, Boaz M, Aizic S, et al. Psychological distress is not associated with treatment failure in patients with gastroesophageal reflux disease. *J Psychosom Res* 2013;75:462–466.
 142. Mizyed I, Fass SS, Fass R. Review article: gastro-oesophageal reflux disease and psychological comorbidity. *Aliment Pharmacol Ther* 2009;29:351–358.
 143. Fass R, Naliboff BD, Fass SS, et al. The effect of auditory stress on perception of intraesophageal acid in patients with gastroesophageal reflux disease. *Gastroenterology* 2008;134:696–705.
 144. Fass R, Fass SS. Psychological comorbidity and chronic heartburn: which is the chicken and which is the egg? *Dig Dis Sci* 2017;62:823–825.
 145. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. *Gut* 2012;61:1340–1354.
 146. Fass R. Therapeutic options for refractory gastroesophageal reflux disease. *J Gastroenterol Hepatol* 2012;27(Suppl 3):3–7.

147. Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. *Gut* 2009;58:295–309.
148. Hershcovici T, Fass R. Management of gastroesophageal reflux disease that does not respond well to proton pump inhibitors. *Curr Opin Gastroenterol* 2010;26:367–378.
149. Fass R, Gasiorowska A. Refractory GERD: what is it? *Curr Gastroenterol Rep* 2008;10:252–257.
150. Martinez SD, Malagon IB, Garewal HS, et al. Non-erosive reflux disease (NERD)—acid reflux and symptom patterns. *Aliment Pharmacol Ther* 2003;17:537–545.
151. Savarino E, Zentilin P, Tutuian R, et al. Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. *J Gastroenterol* 2012;47:159–168.
152. Savarino E, Marabotto E, Zentilin P, et al. The added value of impedance-pH monitoring to Rome III criteria in distinguishing functional heartburn from non-erosive reflux disease. *Dig Liver Dis* 2011;43:542–547.
153. Roman S, Keefer L, Imam H, et al. Majority of symptoms in esophageal reflux PPI non-responders are not related to reflux. *Neurogastroenterol Motil* 2015;27:1667–1674.
154. Poh CH, Gasiorowska A, Navarro-Rodriguez T, et al. Upper GI tract findings in patients with heartburn in whom proton pump inhibitor treatment failed versus those not receiving antireflux treatment. *Gastrointest Endosc* 2010;71:28–34.
155. Boeckxstaens G, El-Serag HB, Smout AJ, et al. Symptomatic reflux disease: the present, the past and the future. *Gut* 2014;63:1185–1193.
156. Kahrilas PJ, Keefer L, Pandolfino JE. Patients with refractory reflux symptoms: What do they have and how should they be managed? *Neurogastroenterol Motil* 2015;27:1195–1201.
157. Herregods TV, Bredenoord AJ, Smout AJ. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. *Neurogastroenterol Motil* 2015;27:1202–1213.
158. Gasiorowska A, Navarro-Rodriguez T, Wendel C, et al. Comparison of the degree of duodenogastroesophageal reflux and acid reflux between patients who failed to respond and those who were successfully treated with a proton pump inhibitor once daily. *Am J Gastroenterol* 2009;104:2005–2013.
159. Dickman R, Maradey-Romero C, Fass R. The role of pain modulators in esophageal disorders—no pain no gain. *Neurogastroenterol Motil* 2014;26:603–610.
160. Clouse RE, Lustman PJ, Eckert TC, et al. Low-dose trazodone for symptomatic patients with esophageal contraction abnormalities. A double-blind, placebo-controlled trial. *Gastroenterology* 1987;92:1027–1036.
161. Cannon RO 3rd, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994;330:1411–1417.
162. Cox ID, Hann CM, Kaski JC. Low dose imipramine improves chest pain but not quality of life in patients with angina and normal coronary angiograms. *Eur Heart J* 1998;19:250–254.
163. Limsrivilai J, Charatcharoenwittaya P, Pausawasdi N, et al. Imipramine for treatment of esophageal hypersensitivity and functional heartburn: a randomized placebo-controlled trial. *Am J Gastroenterol* 2016;111:217–224.
164. Park SW, Lee H, Lee HJ, et al. Low-dose amitriptyline combined with proton pump inhibitor for functional chest pain. *World J Gastroenterol* 2013;19:4958–4965.
165. You LQ, Liu J, Jia L, et al. Effect of low-dose amitriptyline on globus pharyngeus and its side effects. *World J Gastroenterol* 2013;19:7455–7460.
166. Varia I, Logue E, O'Connor C, et al. Randomized trial of sertraline in patients with unexplained chest pain of noncardiac origin. *Am Heart J* 2000;140:367–372.
167. Keefe FJ, Shelby RA, Somers TJ, et al. Effects of coping skills training and sertraline in patients with non-cardiac chest pain: a randomized controlled study. *Pain* 2011;152:730–741.
168. Doraiswamy PM, Varia I, Hellegers C, et al. A randomized controlled trial of paroxetine for noncardiac chest pain. *Psychopharmacol Bull* 2006;39:15–24.
169. Spinhoven P, Van der Does AJ, Van Dijk E, et al. Heart-focused anxiety as a mediating variable in the treatment of noncardiac chest pain by cognitive-behavioral therapy and paroxetine. *J Psychosom Res* 2010;69:227–235.
170. Broekaert D, Fischler B, Sifrim D, et al. Influence of citalopram, a selective serotonin reuptake inhibitor, on oesophageal hypersensitivity: a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2006;23:365–370.
171. 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;26:670–678.
172. Lee H, Kim JH, Min BH, et al. Efficacy of venlafaxine for symptomatic relief in young adult patients with functional chest pain: a randomized, double-blind, placebo-controlled, crossover trial. *Am J Gastroenterol* 2010;105:1504–1512.
173. Rao SS, Mudipalli RS, Remes-Troche JM, et al. Theophylline improves esophageal chest pain—a randomized, placebo-controlled study. *Am J Gastroenterol* 2007;102:930–938.
174. Kirch S, Gegg R, Johns MM, et al. Globus pharyngeus: effectiveness of treatment with proton pump inhibitors and gabapentin. *Ann Otol Rhinol Laryngol* 2013;122:492–495.
175. Clouse RE, Lustman PJ. Use of psychopharmacological agents for functional gastrointestinal disorders. *Gut* 2005;54:1332–1341.
176. Rodriguez-Stanley S, Ciociola AA, Zubaidi S, et al. A single dose of ranitidine 150 mg modulates oesophageal acid sensitivity in patients with functional heartburn. *Aliment Pharmacol Ther* 2004;20:975–982.
177. Rodriguez-Stanley S, Zubaidi S, Proskin HM, et al. Effect of tegaserod on esophageal pain threshold, regurgitation, and symptom relief in patients with functional heartburn and mechanical sensitivity. *Clin Gastroenterol Hepatol* 2006;4:442–450.

178. Basu P, Hempole H, Krishnaswamy N. The effect of melatonin in functional heartburn: a randomized, placebo-controlled clinical trial. *Op J Gastroenterol* 2014; 2014:56–61.
179. Riehl ME, Pandolfino JE, Palsson OS, et al. Feasibility and acceptability of esophageal-directed hypnotherapy for functional heartburn. *Dis Esophagus* 2016;29:490–496.
180. Marrero JM, de Caestecker JS, Maxwell JD. Effect of famotidine on oesophageal sensitivity in gastro-oesophageal reflux disease. *Gut* 1994;35:447–450.
181. Mainie I, Tutuian R, Agrawal A, et al. Combined multi-channel intraluminal impedance-pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. *Br J Surg* 2006; 93:1483–1487.
182. Broeders JA, Bredenoord AJ, Hazebroek EJ, et al. Effects of anti-reflux surgery on weakly acidic reflux and belching. *Gut* 2011;60:435–441.
183. Viazis N, Keyoglou A, Kanellopoulos AK, et al. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: a randomized, double-blind, placebo-controlled study. *Am J Gastroenterol* 2012; 107:1662–1667.
184. Dickman R, Schiff E, Holland A, et al. Clinical trial: acupuncture vs. doubling the proton pump inhibitor dose in refractory heartburn. *Aliment Pharmacol Ther* 2007; 26:1333–1344.
185. Casale M, Sabatino L, Moffa A, et al. Breathing training on lower esophageal sphincter as a complementary treatment of gastroesophageal reflux disease (GERD): a systematic review. *Eur Rev Med Pharmacol Sci* 2016; 20:4547–4552.
186. Maradey-Romero C, Fass R. New and future drug development for gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2014;20:6–16.
187. Maradey-Romero C, Kale H, Fass R. Nonmedical therapeutic strategies for nonerosive reflux disease. *J Clin Gastroenterol* 2014;48:584–589.
188. Andersson K, Carlsson E. Potassium-competitive acid blockade: a new therapeutic strategy in acid-related diseases. *Pharmacol Ther* 2005;108:294–307.
189. Echizen H. The first-in-class potassium-competitive acid blocker, vonoprazan fumarate: pharmacokinetic and pharmacodynamic considerations. *Clin Pharmacokinet* 2016;55:409–418.
190. Ashida K, Sakurai Y, Hori T, et al. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. *Aliment Pharmacol Ther* 2016;43:240–251.
191. Dent J, Kahrilas PJ, Hatlebakk J, et al. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. *Am J Gastroenterol* 2008;103:20–26.
192. Morrison T. Ironwood Pharmaceuticals. Ironwood reports positive top-line data from exploratory Phase IIa trial of IW-3718 in refractory gastroesophageal reflux disease. Available at: <http://investor.ironwoodpharma.com/releasedetail.cfm?ReleaseID=894586>.
193. Topuz U, Umutoglu T, Bakan M, et al. Anesthetic management of the SRS Endoscopic Stapling System for gastro-esophageal reflux disease. *World J Gastroenterol* 2013;19:319–320.
194. Zacherl J, Roy-Shapira A, Bonavina L, et al. Endoscopic anterior fundoplication with the Medigus Ultrasonic Surgical Endostapler (MUSE) for gastroesophageal reflux disease: 6-month results from a multi-center prospective trial. *Surg Endosc* 2015;29:220–229.
195. Ganz RA, Fallon E, Wittchow T, et al. A new injectable agent for the treatment of GERD: results of the Durasphere pilot trial. *Gastrointest Endosc* 2009; 69:318–323.
196. Ellis F, Berne TV, Settevig K. The prevention of experimentally induced reflux by electrical stimulation of the distal esophagus. *Am J Surg* 1968;115:482–487.
197. Clarke JO, Jagannath SB, Kalloo AN, et al. An endoscopically implantable device stimulates the lower esophageal sphincter on demand by remote control: a study using a canine model. *Endoscopy* 2007;39:72–76.
198. Sanmiguel CP, Hagiike M, Mintchev MP, et al. Effect of electrical stimulation of the LES on LES pressure in a canine model. *Am J Physiol Gastrointest Liver Physiol* 2008;295:G389–G394.
199. Rodriguez L, Rodriguez P, Neto MG, et al. Short-term electrical stimulation of the lower esophageal sphincter increases sphincter pressure in patients with gastro-esophageal reflux disease. *Neurogastroenterol Motil* 2012;24:446–450, e213.
200. Rodriguez L, Rodriguez P, Gomez B, et al. Electrical stimulation therapy of the lower esophageal sphincter is successful in treating GERD: final results of open-label prospective trial. *Surg Endosc* 2013;27:1083–1092.
201. Rodriguez L, Rodriguez P, Gomez B, et al. Long-term results of electrical stimulation of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease. *Endoscopy* 2013;45:595–604.

Received June 19, 2017. Accepted July 31, 2017.

Reprint requests

Address requests for reprints to: Ronnie Fass, MD, Division of Gastroenterology and Hepatology, Esophageal and Swallowing Center, Case Western Reserve University, MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, Ohio 44109. e-mail: ronnie.fass@gmail.com; fax: (216) 778-2074.

Conflicts of interest

R.F. is an advisor to Ironwood, Mederi Therapeutics and Ethicon. Speaker for AstraZeneca, Takeda and Mederi Therapeutics and receives a research grant from Ironwood. C.P.G. is an advisor to Torax, Ironwood, Medtronic and Diversatek. Speaker for Medtronic and Diversatek.