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Management of Gastroesophageal Reflux Disease

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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, H_2 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.**

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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 nonobese 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 abnormal[42]; 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 cough[60] and laryngeal symptoms[61] 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 H_2 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
Clostridium difficile 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–.124) 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 varies[87]; 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 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

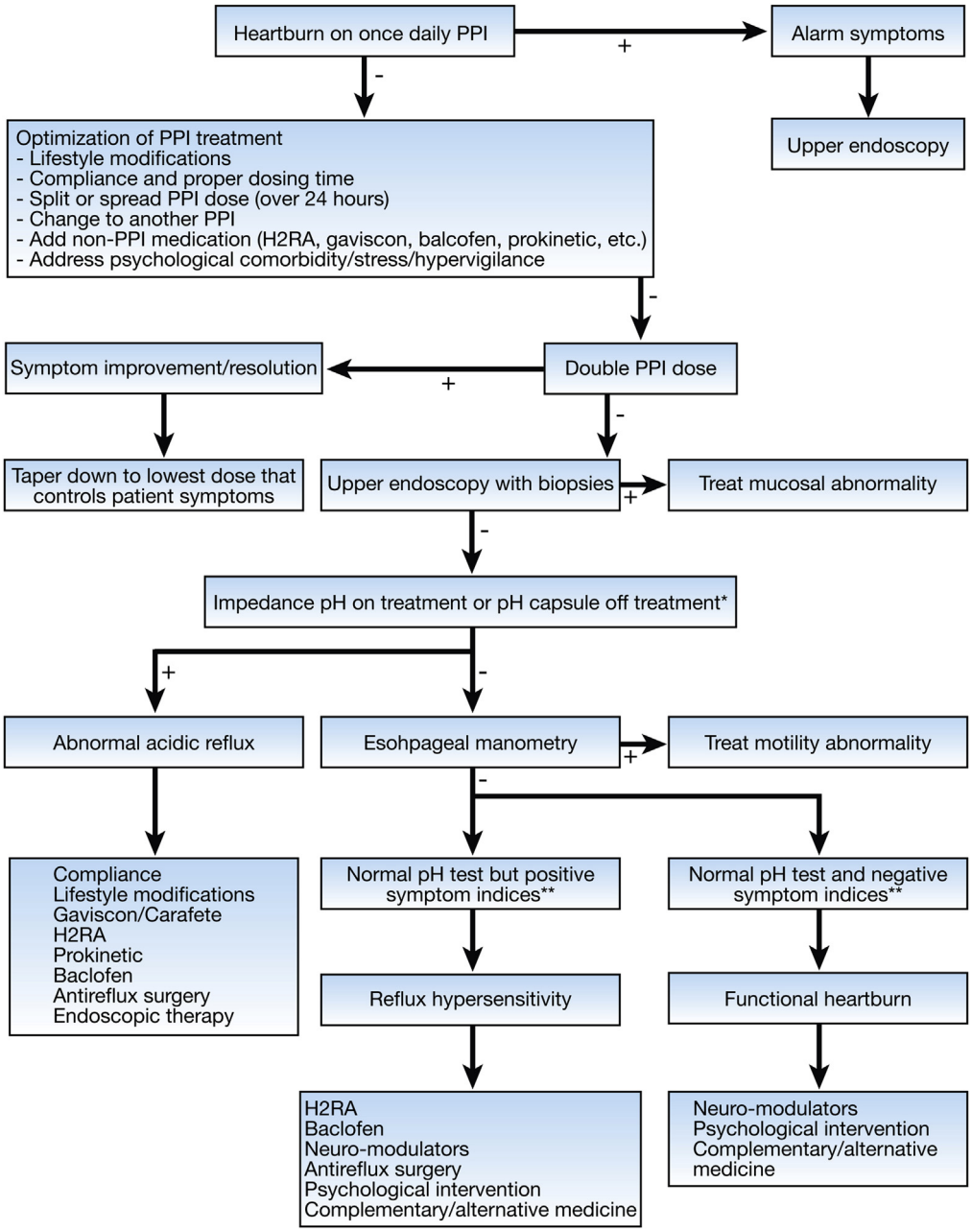

Figure 1. Algorithm for evaluation and management of patients who do not respond to PPI therapy. Initially, once-daily PPI therapy is optimized, with consideration of twice-daily PPI therapy. Objective testing with endoscopy and ambulatory reflux monitoring can identify patients with proven GERD (which 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 PPIs[5] (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 therapy[130]; 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-naive 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]	SRIs	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 patients[190]; 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 nonpharmacologic 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.

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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.