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Diagnosis and Management of Refractory Gastroesophageal Reflux Disease

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Abstract: In up to half of patients with symptoms suspected to stem from gastroesophageal reflux disease (GERD), these symptoms persist despite treatment with daily proton pump inhibitor (PPI) therapy. The symptoms may be characterized as typical (eg, heartburn or regurgitation) or atypical (eg, chest pain or cough). These refractory symptoms, which are frequently encountered in clinical practice, may stem from GERD as well as non-GERD etiologies. Among those patients with objective GERD proven on esophagogastroduodenoscopy (EGD) and/or ambulatory reflux testing, approximately one-fifth may manifest suboptimal symptom response to PPI therapy. After introducing the initial evaluation of patients with suspected GERD symptoms, this article discusses approaches to the esophageal diagnostic workup of patients with refractory symptoms in the setting of proven GERD, focusing on EGD, high-resolution manometry (HRM), and pH-impedance monitoring during treatment with PPI therapy. EGD evaluates for esophagitis, peptic stricture, and hiatal hernia, as well as eosinophilic esophagitis. HRM rules out confounding esophageal motor disorders, identifies behavioral disorders, characterizes the antireflux barrier, and assesses esophageal contractile reserve to help tailor potential antireflux interventions. pH-impedance monitoring during treatment with PPI therapy can help distinguish between PPI-refractory GERD—as evidenced by pathologic acid exposure despite PPI therapy and/or excess burden of reflux events regardless of acidity—and PPI-controlled GERD. This article also discusses potential approaches for patients with symptoms stemming from refractory GERD, encompassing lifestyle, pharmacologic, endoscopic, and surgical management options.

Keywords
Ambulatory reflux monitoring, pH-impedance monitoring, antireflux surgery, functional lumen imaging probe, esophageal motility, gastroesophageal reflux disease

Symptoms suspicious for gastroesophageal reflux disease (GERD) represent one of the most common indications for outpatient presentation to primary care and gastroenterology providers. When symptoms may potentially be attributable to GERD, patients and/or providers often trial over-the-counter or prescription antacids and/or proton pump inhibitors (PPIs). However, population-based survey

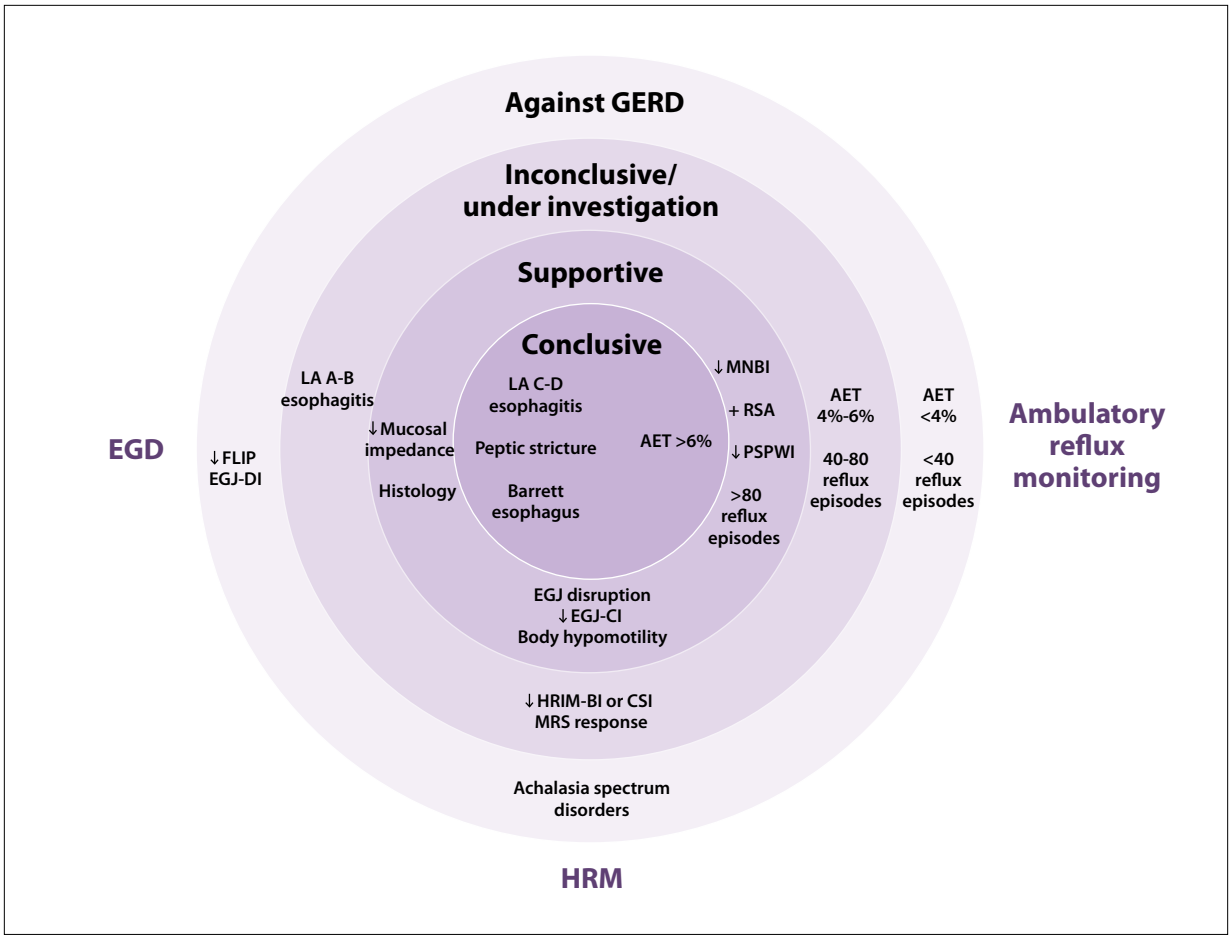

Figure 1. Diagnostic evidence for GERD. Moving from the outer ring toward the center, findings on esophageal diagnostic testing (EGD, HRM, ambulatory reflux monitoring) that (1) suggest against the presence of GERD, (2) are inconclusive and/or warrant further investigation for clinical use, (3) are supportive of or add confidence to a diagnosis of GERD, and (4) represent strong evidence for a diagnosis of GERD; any one of the findings in the innermost circle defines proven GERD.

AET, acid exposure time; CSI, contractile segment impedance; EGD, esophagogastroduodenoscopy; EGJ, esophagogastric junction; EGJ-CI, esophagogastric junction–contractile integral; FLIP EGJ-DI, functional lumen imaging probe esophagogastric junction–distensibility index; GERD, gastroesophageal reflux disease; HRIM-BI, high-resolution impedance manometry–baseline impedance; HRM, high-resolution manometry; LA, Los Angeles classification of reflux esophagitis; MNBI, mean nocturnal baseline impedance; MRS, multiple rapid swallows; PSPWI, postreflux swallow-induced peristaltic wave indices; RSA, reflux-symptom association.

data suggest that in up to half of patients with suspected GERD symptoms, these symptoms may persist despite daily PPI use.[1] Diagnostic evaluation is indicated for further investigation of symptoms in several scenarios, such as when symptoms are nonresponsive or only partially responsive to a regular PPI dose taken appropriately for at least 4 to 8 weeks (ie, refractory symptoms, which may or may not be related to GERD), when alarm symptoms (eg, dysphagia, anemia, bleeding, unintentional weight loss) are present, and when symptoms are atypical for GERD (eg, chest pain, cough, or extraesophageal symptoms, as opposed to typical heartburn and/or regurgitation).[2,3]

In this setting, the diagnostic evaluation may include esophagogastroduodenoscopy (EGD), ambulatory reflux monitoring, and/or esophageal high-resolution manometry (HRM) (Figure 1). EGD is generally the initial test performed. GERD is confirmed when an EGD shows findings of advanced esophagitis (Los Angeles [LA] grades C-D), reflux-mediated esophageal strictures, or biopsy-proven long-segment (>3 cm) Barrett esophagus. In the absence of these findings, ambulatory reflux monitoring should then be performed while the patient is not receiving PPI therapy.[2,4] If available, the preferred modality is prolonged wireless reflux monitoring for up to 96 hours. Ambulatory reflux monitoring (performed while the patient is not receiving PPI therapy) that shows a distal esophageal acid exposure time (AET) exceeding 6% also represents conclusive evidence of GERD.[4]

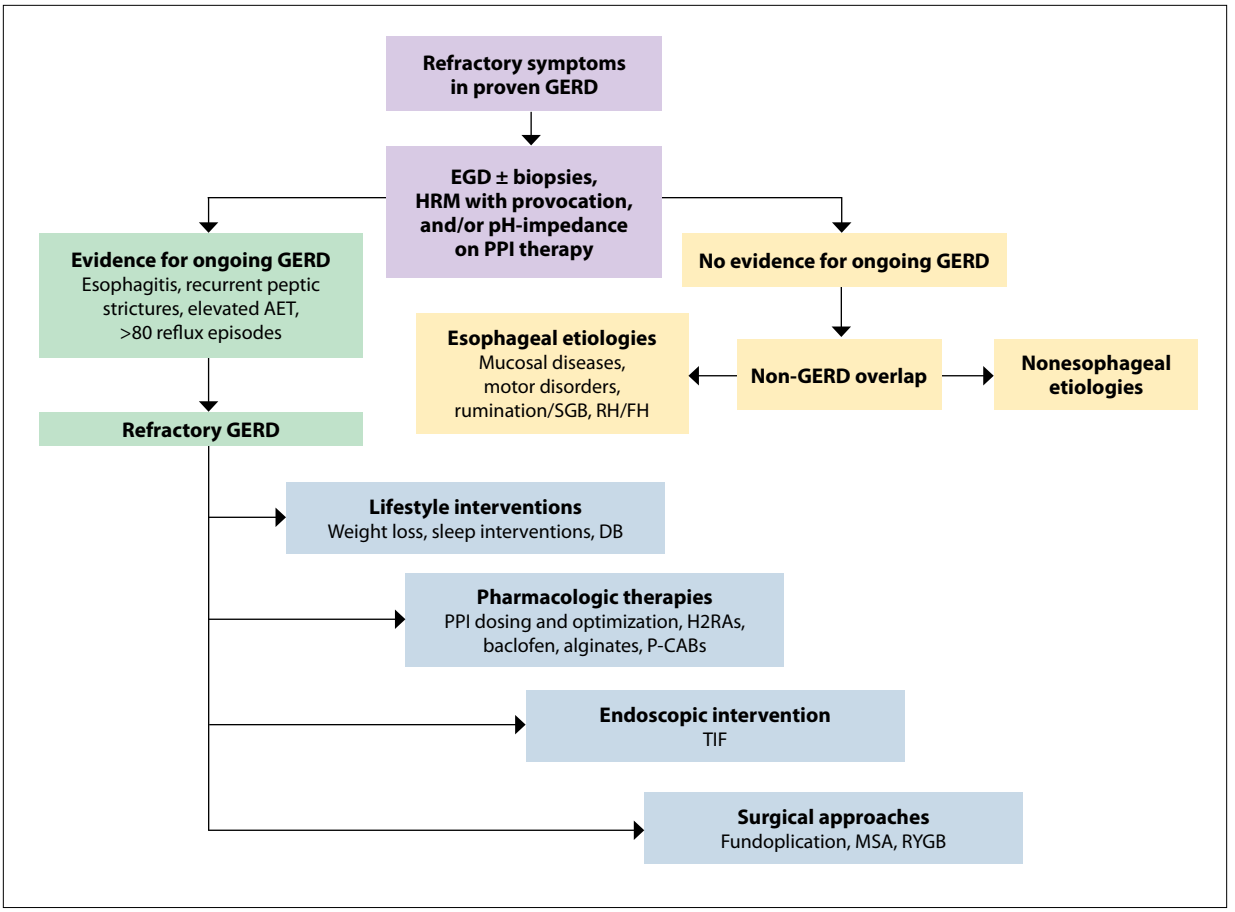

Figure 2. Clinical algorithm for the evaluation of refractory symptoms in the setting of proven GERD.[3] Advanced LA-grade esophagitis, biopsy-proven Barrett esophagus, reflux-mediated esophageal stricture, or AET exceeding 6% on ambulatory reflux monitoring constitutes proven GERD. The workup for refractory symptoms in this setting should include an EGD with consideration of esophageal biopsies, HRM with potential provocative maneuvers, and, in certain cases, pH-impedance monitoring performed during treatment with PPIs.

AET, acid exposure time; DB, diaphragmatic breathing; EGD, esophagogastroduodenoscopy; FH, functional heartburn; GERD, gastroesophageal reflux disease; H2RAs, histamine type-2 receptor antagonists; HRM, high-resolution manometry; LA, Los Angeles classification of reflux esophagitis; MSA, magnetic sphincter augmentation; P-CABs, potassium-competitive acid blockers; PPI, proton pump inhibitor; RH, reflux hypersensitivity; RYGB, Roux-en-Y gastric bypass; SGB, supragastric belching; TIF, transoral incisionless fundoplication.

In patients with proven GERD (supported by objective evidence), the presence of symptoms refractory to appropriate PPI administration is termed refractory GERD symptoms, with unclear associations with ongoing reflux.[3,5] As recommended in the recent consensus statement from major motility societies, patients with refractory typical or atypical symptoms despite PPI therapy in the setting of proven GERD warrant further diagnostic assessment to distinguish whether the symptoms stem from ongoing (inadequately controlled) GERD or from overlap with non-GERD and/or nonesophageal processes.[3] This assessment should include a high-quality EGD (if not recently performed) with consideration of esophageal biopsies, HRM with potential provocative maneuvers, and, in certain cases, pH-impedance monitoring performed while the patient is receiving PPI therapy (Figure 2).

Diagnosis

Esophagogastroduodenoscopy

In this setting, the patient should undergo high-quality EGD (if not recently performed). Alternate mucosal etiologies for symptoms, such as eosinophilic esophagitis, lymphocytic esophagitis, infectious esophagitis, pill esophagitis, skin disorders involving the esophagus, and malignancy, should be carefully excluded. Prolonged PPI therapy decreases the diagnostic yield of endoscopy; in

one report of patients with heartburn not responsive to once-daily PPI therapy, the likelihood that an endoscopy performed after 8 weeks of PPI therapy would detect esophagitis was 7%.[6] In the setting of optimized PPI use, visualization of esophageal mucosal breaks or ulceration (not attributable to nonreflux etiologies) consistent with advanced esophagitis (likely LA grade B, and definitely LA grades C-D) suggests the presence of refractory GERD, specifically inadequately controlled acid reflux.[3,7] Similarly, given the effectiveness of PPI therapy in the prevention of recurrence, reflux-mediated esophageal strictures that recur despite previous complete dilation and optimized PPI therapy should be considered evidence of inadequately controlled acid reflux.[3,8,9] In contrast, the detection or persistence of Barrett esophagus as assessed by an EGD, which can occur in predisposed individuals with longstanding GERD exposure, does not represent evidence of refractory GERD, as PPI therapy alone does not appear to repair or resolve segments of Barrett esophagus.[10-12]

If not previously performed, esophageal biopsies should be considered in this setting to evaluate for eosinophilic esophagitis, especially if any element of dysphagia is present.[13,14] Eosinophilic esophagitis may be present even when the esophagus appears normal during endoscopy.[15] Studies have shown that 4% to 5% of patients with refractory reflux symptoms had evidence of eosinophilic esophagitis with this approach (acknowledging that the presence of some dysphagia is strongly associated with this finding).[16,17] In contrast, the finding of microscopic inflammation on esophageal biopsies, while potentially an adjunctive element in a GERD diagnosis,[4,18] cannot be considered definitive evidence for refractory GERD in this setting based on the available data. Therefore, routine biopsies are not recommended in the absence of dysphagia or suspicion of a mucosal abnormality.[3]

Although other modalities (including barium esophagography or HRM) may be informative in this regard, EGD can also evaluate for hiatal herniation and esophagogastric junction (EGJ) disruption. In the evaluation of GERD, barium esophagography has very limited utility otherwise; in fact, the presence of gastroesophageal reflux on barium esophagography does not correlate with the incidence or extent of reflux on pH-impedance monitoring.[19] The presence and increasing size of hiatal hernias may be associated with more profound and/or complicated GERD.[20,21] Further, those patients with proven GERD and prominent regurgitation symptoms despite PPI therapy in the setting of a large hiatal hernia have a high pretest probability that refractory GERD is generating symptoms, and therefore pH-impedance monitoring on PPI therapy may not be routinely required in this subpopulation.[3] Concordantly, prominent regurgitation responds more favorably to antireflux surgery (ARS) than other reflux symptoms, and expert panels suggest that ARS represents a reasonable management option in this context.[22-24]

The esophageal functional lumen imaging probe (FLIP), performed at the time of a sedated EGD, utilizes impedance planimetry technology with distension of a catheter-mounted balloon to different volumes to evaluate esophageal dimensions and pressures.[25,26] Increasing data support the utility of the FLIP in the evaluation of nonobstructive dysphagia and the management of potential achalasia spectrum disorders (for which the EGJ distensibility index is abnormally low). Further, EGJ distensibility indices may be helpful in intraoperative decision-making regarding wrap size and/or crural closure at antireflux interventions, although further data are needed to incorporate the FLIP into routine practice in this context.[27] Otherwise, EGJ distensibility index values have not reliably segregated patients with GERD from controls in a manner warranting their inclusion in the diagnostic approach to refractory GERD.[28]

High-Resolution Manometry

Although not a conclusive diagnostic test for GERD, esophageal HRM assesses motor function and localizes the lower esophageal sphincter for placement of reflux catheters, and should be performed for symptom evaluation in patients with GERD as well as prior to initiation of invasive treatment.[29-31] Especially in the setting of incomplete symptom response with PPI therapy, HRM rules out potential confounding esophageal motor disorders, such as achalasia spectrum or hypercontractile disorders, that may present with symptoms similar to GERD.[32-34] Further, HRM helps to identify any potential motor contraindications, such as absent contractility, to standard fundoplication.[35] In addition to evaluating for hiatal hernia, HRM can assess the antireflux barrier via the novel EGJ-contractile integral metric, which may segregate patients with GERD from controls, and quantify changes from surgical intervention.[4,36-38] Recent data suggest that distal esophageal impedance values acquired from the landmark phase or during contractions on high-resolution impedance manometry have potential utility in the assessment of reflux burden, but these metrics are typically extracted from testing performed while patients are not receiving PPI therapy and warrant further investigation for clinical use.[39-41]

In particular, 2 provocative manometric maneuvers—postprandial high-resolution impedance manometry and multiple rapid swallow sequences—may afford significant insights into patients with refractory symptoms in this setting.[42] For patients with suspicious refractory symptoms that persist despite PPI therapy, especially

regurgitation and/or belching, extended monitoring with high-resolution impedance manometry for 60 to 90 minutes after consumption of a meal may reveal the presence of behavioral disorders generating symptoms that overlap with or mimic those of GERD.[34,43-45] Among 94 patients without a PPI response referred for evaluation with postprandial high-resolution impedance manometry, evidence was suggestive of supragastric belching in 42% and of rumination patterns in 20%.[46]

Multiple rapid swallow sequences are easily performed during the HRM protocol by administering five 2-mL swallows less than 3 seconds apart while the patient is in the supine position. This test facilitates evaluation of esophageal contractile reserve by comparing the post–multiple rapid swallow contractile vigor (quantified by the distal contractile integral [DCI]) to that of the mean DCI from the single wet swallows. A ratio higher than 1 indicates the presence of contractile reserve.[30,47] Among patients with heartburn with unrevealing results from EGD and HRM, the multiple rapid swallow response is inversely associated with acid reflux burden.[48] Further, abnormal preoperative multiple rapid swallow responses (without DCI augmentation) predict late postoperative dysphagia after fundoplication, and these responses may help distinguish among phenotypes of evolving ineffective esophageal motility with laparoscopic ARS.[47,49-51] Therefore, among patients with refractory GERD for whom ARS is being considered, the inclusion of multiple rapid swallow sequences in the preoperative HRM protocol can help tailor fundoplication (ie, complete vs partial wrap) to minimize the risks of postoperative dysphagia.

Ambulatory Reflux Monitoring

Ambulatory reflux monitoring is traditionally performed with either catheter-based (pH or combined pH-impedance) or wireless pH testing modalities. In the absence of objective evidence of GERD on an EGD, ambulatory reflux monitoring should initially be performed when the patient is not receiving a PPI.[2] Distal esophageal AET refers to the percentage of time the pH is below 4 during the monitoring period. AET represents the most reproducible and evidence-based clinical metric for reflux burden and for prediction of symptomatic response with antireflux therapies.[52-54] Specifically, per the Lyon Consensus, an AET higher than 6% on ambulatory reflux monitoring performed while the patient is not receiving a PPI represents objective evidence of GERD, whereas an AET of 4% to 6% may be considered inconclusive.[4] AET also predicts for the ability to discontinue PPI therapy in patients with typical reflux symptoms without symptom escalation; accordingly, if evidence of GERD is not observed during reflux monitoring, attempts should be made to de-escalate and discontinue PPI therapy.[55]

Particularly when AET is inconclusive, other metrics extracted from reflux monitoring may be helpful. Although their analyses have limitations, positive reflux-symptom association (RSA) indices can be supportive of a GERD diagnosis, and they may predict symptomatic outcomes with antireflux therapies.[53,56,57] In fact, combinations of normal and abnormal AET and RSA can define phenotypes of GERD through reflux monitoring,[58] and RSA segregates reflux hypersensitivity from functional heartburn.[59] Adjunctive metrics from pH-impedance monitoring, such as low distal esophageal mean nocturnal baseline impedance (MNBI) or decreased postreflux swallow-induced peristaltic wave indices (PSPWI), can support a GERD diagnosis. Specifically, distal esophageal baseline impedance values—acquired from resting, nocturnal periods on pH-impedance tracings as the MNBI—may represent a longitudinal marker of reflux burden based on mucosal integrity because these values negatively correlate with AET and independently predict symptomatic outcomes with antireflux therapy, even when AET is inconclusive.[60,61] PSPWI—calculated as the proportion of reflux events that are followed by a postreflux swallow-induced peristaltic wave within 30 seconds across a pH-impedance study—assesses chemical clearance, and can stratify patients with erosive reflux disease, nonerosive reflux disease, and functional heartburn, increasing the accuracy of the GERD diagnosis.[62] Further, per the Lyon Consensus, elevated total numbers of reflux episodes (>80/24 hours) should be considered abnormal and suggestive of GERD, whereas less than 40 reflux episodes per 24 hours may be considered physiologic (Figure 1).[4,63]

In patients with proven GERD with persistent symptoms despite appropriate PPI therapy, pH-impedance monitoring can be performed during administration of double-dose therapy for further evaluation, especially for assessment of inadequate acid suppression or evidence supporting RSA.[3,4] Combined pH-impedance technology provides value in this setting, as it can detect weakly acidic or nonacidic reflux that would not be identified by pH monitoring alone, without the addition of impedance sensors.[64] Although data supporting the utility of and thresholds for AET are robust for reflux monitoring performed in patients not receiving PPIs, normative data are currently limited for testing performed during treatment with PPIs, and lower thresholds for AET in this setting may suggest refractory GERD. As PPI therapy reduces the acidity of refluxate but does not prevent reflux events, assessment of weakly acidic reflux episodes is of particular interest for patients with persistent prominent regurgitation symptoms.[65,66] Elevated total numbers of reflux episodes (considered >80/24 hours) predict symptomatic outcomes from antireflux interventions in patients with regurgitation-predominant GERD, and normalization of

these numbers of reflux episodes with such interventions corresponds with successful symptomatic outcomes.[63] However, rumination syndrome and delayed gastric emptying should be carefully evaluated in these patients as potential contributors to symptoms.[43]

Overlap esophageal syndromes (eg, reflux hypersensitivity, functional heartburn, functional chest pain) in the setting of proven GERD may contribute prominently to symptoms in patients with suboptimal responses to PPI therapy through visceral hypersensitivity and/or hypervigilance mechanisms.[3] In this context of pH-impedance monitoring performed in patients receiving PPI therapy who have a physiologic AET and normal total number of reflux episodes, positive RSA indices may indicate overlap reflux hypersensitivity with proven GERD. Reflux hypersensitivity is likely best characterized as a heterogeneous entity, for which different populations may benefit from central neuromodulation, behavioral interventions, or GERD-directed therapies.[59,67] Interestingly, almost half of patients with this diagnosis may have behavioral disorders, such as rumination syndrome or supragastric belching.[68] These disorders can be identified via postprandial high-resolution manometric monitoring, and have therapeutic implications.[68] In patients with proven GERD who undergo pH-impedance monitoring during PPI therapy, if AET and the total number of reflux episodes are physiologic, and the RSA is negative, persistent GERD can likely be ruled out as a cause of symptoms.[3,59] Instead, overlap functional esophageal disorders may be present, which should prompt alternative management considerations, such as central neuromodulation and/or psychologic approaches.[3,59]

Management

Lifestyle Interventions

Patients with GERD should be counseled on lifestyle and behavioral approaches that may offer benefit for symptomatic disease. Although many patients with GERD may report that certain foods can precipitate their symptoms, there is a paucity of data to support the symptomatic benefit of broader dietary restrictions.[69,70] Avoiding late-evening, larger meals close to bedtime may improve supine acid exposure, particularly in patients with bothersome nocturnal symptoms.[71] Likewise, sleep interventions may improve nocturnal reflux and associated symptoms, particularly in patients with hiatal hernia.[70,72,73] Particularly helpful strategies may include elevation of the head of the bed and/or sleeping in the left lateral position (to potentially assist with acid clearance by helping to position the EGJ above the level of pooled acid), facilitated through props such as wedges, blocks under bedposts, or dedicated pillows.[70,72,73]

Extensive data support the association between a high body mass index (BMI) and GERD symptoms.[74] Further, the preponderance of data examining this relationship indicates that weight loss appears to improve esophageal acid exposure and reflux symptoms, likely in a dose-dependent fashion.[75,76] Interestingly, weight loss appears to improve symptoms of GERD regardless of the initial BMI, suggesting benefits even for nonobese patients.[77]

Evidence supporting alcohol abstinence or smoking cessation for the purposes of managing refractory GERD symptoms is more limited. Although there are extensive data showing that such interventions have myriad other, larger positive effects on health, their relationships with GERD are less clear. Older data suggested that esophageal acid exposure was not associated with smoking status nor the actual act of smoking.[78,79] Based on case control data from Norwegian public health surveys, alcohol did not appear to represent a risk factor for reflux symptoms, but tobacco smoking was associated with reflux symptoms in a dose-dependent fashion.[80] German data found that both smoking and the consumption of spirits were associated with increased reflux symptoms.[81] Finally, analysis of Norwegian data suggested that smoking cessation may be associated with improvement in severe reflux symptoms among patients with normal BMI; however, this association was not present among overweight individuals.[82]

Diaphragmatic breathing, which is commonly utilized for rumination syndrome, may also carry benefits for proven GERD. A recent study evaluated diaphragmatic breathing in this context, utilizing postprandial high-resolution impedance manometry, in patients with upright GERD (proven on reflux monitoring).[83] The trial randomized patients and control subjects to diaphragmatic breathing or a sham technique, followed by 48 hours of pH-impedance monitoring, with half of the patients randomized to postprandial diaphragmatic breathing on the second day of monitoring.[83] In this study, postprandial diaphragmatic breathing decreased the number of postprandial reflux events in patients and controls, compared with observation. Further, patients randomly assigned to diaphragmatic breathing had lower esophageal acid exposure in a 2-hour window postprandially on day 2 (after diaphragmatic breathing) compared with day 1 (without diaphragmatic breathing). These data are preliminary but promising, and further investigations into the utility of diaphragmatic breathing in the management of GERD and refractory GERD are warranted.

Pharmacologic Therapies

PPIs, which are widely used as the foundation of medical management for GERD, should be optimized in the setting of refractory symptoms. Based on their pharmacokinetic and pharmacodynamic properties (including the

need for gastric emptying to facilitate absorption from the small bowel), PPIs are most effective in the control of intragastric pH and GERD symptoms when taken prior to meals.[3] For once-daily dosing, PPIs should ideally be taken 30 to 60 minutes prior to breakfast; for twice-daily dosing, the second dose should be taken 30 to 60 minutes prior to dinner. Split (twice-daily) PPI dosing maintains intragastric pH above 4 for higher proportions of the day compared with standard (once-daily) dosing, with this control of intragastric pH serving as a surrogate marker for clinical endpoints.[84] Clinicians should confirm that their patients with refractory GERD are adherent to PPIs. In patients with refractory GERD, particularly those with persistent esophagitis or elevated esophageal acid exposure, PPI therapy should be optimized with a more potent PPI, a higher-dose PPI, and/or twice-daily administration, in order to maximize the proportion of the day that the intragastric pH is higher than 4.[3] There appear to be negligible differences among PPIs in terms of symptom relief or healing in patients with erosive esophagitis based on a meta-analysis.[85] The different PPIs may vary in their ability to suppress acid based on the proportion of time the intragastric pH is higher than 4. However, with twice-daily dosing, even the relatively least potent PPI (pantoprazole 20 mg) equaled or exceeded the effectiveness of the higher doses of the most potent PPIs (rabeprazole 40 mg or omeprazole-equivalent 72 mg) given once daily, in terms of the proportion of time during which intragastric pH was above 4.[84]

Potassium-competitive acid blockers (P-CABs) inhibit proton pump potassium–exchange channels to more rapidly elevate intragastric pH compared with PPIs. However, P-CABs are not available for clinical use in the United States at this time. Compared with once-daily esomeprazole at 40 mg, the P-CAB tegoprazan more effectively and durably suppressed acid among healthy volunteers, based on intragastric pH monitoring.[86] The P-CAB vonoprazan, administered at 20 mg once daily, was numerically superior to lansoprazole (30 mg once daily) in healing severe (LA grades C-D) erosive esophagitis at 2 weeks (88% vs 64%), 4 weeks (96% vs 81%), and 8 weeks (99% vs 88%).[87] Further data, especially in Western populations, and the regulatory approval to utilize P-CABs in the clinical setting may facilitate the inclusion of these agents among the treatment options for symptoms attributable to refractory GERD in the United States.

There is limited evidence to support the routine use of nocturnal histamine type-2 receptor antagonists (H2RAs) as adjunctive therapy to PPI regimens for refractory nighttime symptoms. H2RAs are inferior to PPIs for acid suppression, but may enhance the duration of acid suppression in an adjunct role to decrease the prevalence of nocturnal acid breakthrough.[88,89] However, the use of supplemental H2RAs in this manner is associated with tachyphylaxis, and no differences in acid suppression were found when twice-daily PPIs were administered alone or with H2RAs given at bedtime after 1 week of combination therapy, limiting the utility of these agents for longer-term use.[90]

Other medications have also been studied for GERD treatment in potential adjunct roles to PPIs. Baclofen can reduce transient lower esophageal sphincter relaxations (tLESRs) in patients with GERD as well as healthy controls, and may be helpful in an adjunct role to PPIs given its distinct mechanism of action, especially in the setting of prominent regurgitation symptoms.[91,92] However, the use of baclofen may be limited by its frequent dosing and side effects, such as dizziness and/or drowsiness. Further, baclofen is not as readily recommended in patients with hiatal hernia, as the mechanisms of reflux in this setting also involve strain and mechanical properties, as opposed to only tLESRs. Raft-forming alginate preparations may have some symptom benefit in refractory GERD. As an adjunct therapy, alginate antacid improved reflux symptom burden and breakthrough symptoms compared with placebo in patients with PPI-refractory GERD,[93] although other confirmatory data suggested that the additional symptomatic improvement did not differ from that of placebo.[94]

Although some individual studies have suggested potential benefit for the use of prokinetic medications (eg, domperidone, metoclopramide, mosapride, prucalopride) as adjunct therapy to PPIs in GERD, a meta-analysis did not demonstrate significant symptom relief, reduction in esophageal AETs, or healing of erosive esophagitis for combination PPIs plus prokinetic therapy when compared with PPI therapy alone. Instead, there were significant increases in adverse events.[95] Therefore, although prokinetics may augment gastric emptying, they are not recommended in the management of refractory GERD symptoms.[3]

Endoscopic Interventions

Because PPI therapy only reduces the acidity of reflux episodes without stopping the episodes themselves,[66] endoscopic or surgical antireflux interventions may be considered in this setting, particularly for prominent regurgitation symptoms. Data suggest symptomatic benefit with transoral incisionless fundoplication (TIF), performed endoscopically with prototype devices, in some patients with GERD, especially those with regurgitation-predominant symptoms without significant hiatal hernias (>2 cm) or advanced esophagitis. Specifically, among a cohort of patients with persistent symptoms despite 6 months of PPI use who were randomly assigned

to TIF or maximum-dose PPI therapy, those in the TIF arm had improved GERD symptom burden at 6-month follow-up.[96] A meta-analysis of TIF efficacy data demonstrated improvements in symptoms and numbers of reflux events (but not esophageal AET), although PPI usage increased with time, and most patients resumed PPIs (albeit at reduced doses) during longer-term follow-up after TIF.[97]

Radiofrequency application to the distal esophagus has been studied as a potential endoscopic antireflux intervention, with the hope that resultant lower esophageal sphincter hypertrophy may augment lower esophageal sphincter pressure and decrease tLESRs.[70] However, the evidence to support its efficacy has been limited. A meta-analysis of data comparing radiofrequency application to sham procedures or PPI therapy demonstrated no differences in AET, lower esophageal sphincter pressure, ability to discontinue PPIs, or health-related quality of life (HRQL).[22,98]

Surgical Approaches

Traditional ARS, performed laparoscopically with complete or partial fundoplication (laparoscopic fundoplication [LF]), is effective for refractory GERD symptoms.[3] A randomized study of veterans with refractory reflux-related heartburn despite PPI therapy (confirmed with pH-impedance monitoring performed during treatment with PPI therapy) randomly assigned patients to LF (with complete Nissen wrap) or medical treatments (PPIs plus baclofen with or without desipramine, or PPIs plus placebo).[99] Treatment success (based on >50% decrease in GERD-HRQL scores) was significantly higher with LF compared with medical therapy at 1-year follow-up (67% vs 12%-28%).[99] A network meta-analysis comparing LF and TIF suggested that LF had a higher probability of improving AET as compared with PPIs or TIF.[100] An expert panel on management options for patients with GERD and persistent symptoms despite PPIs deemed LF appropriate for patients with breakthrough symptoms in the setting of elevated AET with or without hiatal hernia, and moderately appropriate for patients with a positive RSA for regurgitation and a large hiatal hernia with normal AET.[22] As with any medical treatment or intervention, careful patient selection and a thorough discussion with the patient are paramount, as LF does carry risks, such as dysphagia, wrap disruption or herniation, gas/bloating, and the need for PPI use.[101]

Magnetic sphincter augmentation (MSA) features laparoscopic implantation of a ring of magnets at the EGJ, augmenting the lower esophageal sphincter by reducing the retrograde movement of gastric contents and reflux.[70] A meta-analysis compared outcomes with MSA vs LF in studies that largely excluded patients with significant hiatal hernias.[102] The meta-analysis showed comparable rates of PPI discontinuation in the short term, but superior preservation of the ability to belch and vomit with MSA.[102] A subsequent study that randomly assigned patients with persistent regurgitation despite once-daily PPIs to either MSA or twice-daily PPIs demonstrated significantly higher rates of regurgitation relief (89% vs 10%) with MSA at 6-month follow-up.[103] Although there have been limited cases of long-term dysphagia and device erosion or migration prompting device removal, MSA may represent a laparoscopic antireflux option in refractory GERD, especially for patients with intact esophageal body motility and without larger hiatal hernias.[22]

Although gastric sleeve surgery may worsen GERD symptoms, Roux-en-Y gastric bypass (RYGB) may be considered in morbidly obese patients with refractory GERD.[3] A retrospective review of morbidly obese patients found that RYGB was associated with significantly lower overall in-hospital complications compared with LF, with comparable length of stay and risk-adjusted mortality.[104] Beyond reducing BMI and obesity-associated complications, RYGB reduces GERD symptoms, improves reflux esophagitis, and decreases esophageal acid exposure for longer than 3 years.[105]

Conclusion

Patients with persistent symptoms potentially attributable to GERD that do not resolve with appropriate trials of PPI therapy deserve appropriate evaluation to guide their management. Even in the context of proven GERD (objective evidence of GERD demonstrated on EGD or on ambulatory reflux monitoring), these persistent symptoms do not necessarily or uniformly stem from refractory GERD (Figure 1). Beyond a careful history, the diagnostic workup in this setting should include high-quality EGD if not recently performed, with consideration of esophageal biopsies; HRM with applicable provocative maneuvers (including consideration of postprandial high-resolution impedance manometry if appropriate); and, in certain cases, pH-impedance monitoring performed in patients receiving twice-daily PPI therapy (Figure 2). If this workup rules out other potential etiologies, such as esophageal mucosal diseases, motor disorders, behavioral disorders, or overlap functional disorders that would guide pursuit of appropriate alternate therapeutics, and implicates refractory GERD in symptom generation, clinical management may include reasonable attempts at lifestyle interventions and optimization of pharmacologic therapies. However, persistent refractory GERD symptoms, particularly regurgitation, may prompt consideration of endoscopic or surgical antireflux intervention options, as guided by the clinical scenario and patient preference.

Disclosures

Dr Patel has no relevant conflicts of interest to disclose. Dr Yadlapati is a consultant through an institutional agreement for Medtronic, Ironwood Pharmaceuticals, and Diversatek. She is also a consultant for Phathom Pharmaceuticals. In addition, she has received research support from Ironwood Pharmaceuticals and is a member of the advisory board of RJS Mediagnostix.

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