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Review

Refractory Gastroesophageal Reflux Disease: Diagnosis and Management

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Gastroesophageal reflux disease (GERD) is common, with increasing worldwide disease prevalence and high economic burden. A significant number of patients will remain symptomatic following an empiric proton pump inhibitor (PPI) trial. Persistent symptoms despite PPI therapy are often mislabeled as refractory GERD. For patients with no prior GERD evidence (unproven GERD), testing is performed off antisecretory therapy to identify objective evidence of pathologic reflux using criteria outlined by the Lyon consensus. In proven GERD, differentiation between refractory symptoms (persisting symptoms despite optimized antisecretory therapy) and refractory GERD (abnormal reflux metrics on ambulatory pH impedance monitoring and/or persistent erosive esophagitis on endoscopy while on optimized PPI therapy) can direct subsequent management. While refractory symptoms may arise from esophageal hypersensitivity or functional heartburn, proven refractory GERD requires personalization of the management approach, tapping from an array of non-pharmacologic, pharmacologic, endoscopic, and surgical interventions. Proper diagnosis and management of refractory GERD is critical to mitigate undesirable long-term complications such as strictures, Barrett's esophagus, and esophageal adenocarcinoma. This review outlines the diagnostic workup of patients presenting with refractory GERD symptoms, describes the distinction between unproven and proven GERD, and provides a comprehensive review of the current treatment strategies available for the management of refractory GERD.
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Key Words
Endoscopy; Esophageal pH monitoring; Gastroesophageal reflux; Refractory GERD

Introduction

Gastroesophageal reflux disease (GERD) is a frequently encountered diagnosis in clinical practice, with an estimated prevalence ranging from 8-33% of the general population, and associated economic impact in the United States totaling as much as $10 billion on an annual basis.[1-4] Almost one-third of adults report typical GERD symptoms (ie, heartburn, regurgitation, and esophageal chest pain) on a weekly basis.[5,6] The mainstay of initial GERD management hinges on a proton pump inhibitor (PPI) trial to determine if symptoms improve with effective acid suppression.[5] While approximately two-thirds of patients with erosive esophagitis (EE) and one-half with non-erosive reflux disease (NERD) will achieve symptomatic response with an empiric PPI trial, patients presenting with atypical symptoms, especially laryngeal symptoms such as hoarseness, cough, throat clearing, and sore throat, are much less likely to improve.[3,4,6-8] Although PPI response is utilized

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as a surrogate for diagnostic findings of GERD on objective testing, available literature suggests suboptimal sensitivity (ranging from 71-78%) and specificity (ranging from 44-54%) of a PPI trial when compared to GERD evidence on endoscopy and/or reflux monitoring studies.[3,9,10] Furthermore, symptom relief does not always associate with evidence of pathologic GERD, as symptomatic improvement has been demonstrated in more than one-third of patients with normal upper endoscopy and reflux monitoring, likely related to placebo effect and/or incomplete GERD evidence on 24-hour reflux monitoring.[3,11] Nevertheless, a PPI trial is a pragmatic initial step for typical GERD symptoms, even though as many as 54% of patients will remain symptomatic despite the PPI trial.[3,5,8,12] With the availability of potassium competitive acid blockers (PCABs) that demonstrate highly efficient acid suppression right from the first dose, these agents might replace PPIs as the agents of choice for an initial empiric therapeutic trial.

Persistent symptoms despite acid suppressive therapy may be inappropriately labeled as refractory GERD. Indeed, the literature highlights failure to meet diagnostic criteria for GERD in 47-65% of patients with persistent symptoms despite PPI therapy.[4,8,13] Without confirmatory testing to identify the presence or absence of pathologic reflux, over-diagnosis of GERD is likely, since > 60% of patients who do not respond to a PPI trial do not have abnormal reflux metrics on reflux monitoring performed off therapy.[8,13] In this review, we illustrate the recommended diagnostic evaluation for patients suspected to have refractory GERD and discuss available management strategies in this population.

Definitions

The defining features of GERD include an abnormal reflux monitoring study and/or findings on upper endoscopy that corroborate pathologic acid exposure, such as EE or Barrett's esophagus (BE).[3,4,8,14-16] Unproven GERD indicates that the patient either has not undergone testing to define features that identify objective GERD, or has negative testing while off anti-secretory therapy. In contrast, proven GERD implies that objective evidence of GERD has been previously demonstrated on either endoscopy or ambulatory reflux monitoring.[3,16] Persisting symptoms while on treatment in patients with a history of proven GERD should be referred to as 'refractory symptoms' rather than refractory GERD. Given that symptoms do not necessarily correlate with pathologic reflux, further evaluation can define whether the patient truly has refractory GERD versus esophageal hypersensitivity and/or functional heartburn. This designation is dependent on whether GERD has been previously proven with diagnostic testing.

Much variability exists in the current literature regarding the definition of refractory GERD. Persistent evidence of pathologic reflux (abnormal ambulatory reflux monitoring and/or EE on endoscopy) while on antisecretory therapy defines refractory GERD. Conversely, for patients with proven GERD who have normal pH-impedance monitoring despite symptoms while on optimized PPI treatment, esophageal hypersensitivity, functional heartburn, or an alternate process is the likely culprit.[17,18] The core difference between esophageal hypersensitivity (reflux hypersensitivity) and functional heartburn is determined by presence or absence of reflux-symptom association, which is best assessed using pH-impedance monitoring.[18] Without proper investigation for ongoing symptoms, however, pathologic reflux is difficult to differentiate from esophageal disorders of gut-brain interaction (DGBI).[18]

Evaluation of Refractory Symptoms in Unproven Gastroesophageal Reflux Disease

Diagnostic testing for the objective presence of GERD parameters can direct further management in the patient with persistent symptoms despite empiric acid suppressive therapy (Fig. 1). Evaluation starts with an upper endoscopy to inspect the esophagus for evidence of reflux-related mucosal changes, which consist of high-grade EE categorized using the Los Angeles (LA) grades to B, C, or D, biopsy proven BE, or peptic esophageal stricture.[3,6,15,16] Emerging data indicates that LA grade B esophagitis in symptomatic patients is sufficient for an objective diagnosis of GERD.[3,8,19,20] Optimally, endoscopy is performed after withholding acid suppression for 2-4 weeks whenever possible. Since high-grade esophagitis is only observed in one-third of treatment naive symptomatic patients and in one-tenth of symptomatic patients on acid suppression, further diagnostic evaluation is typically needed if upper endoscopy is unrevealing.[3,21] Low-grade esophagitis (LA grade A esophagitis) can be seen in healthy asymptomatic individuals, and therefore does not constitute conclusive evidence of GERD. Recent data indicates that histopathology has a low diagnostic yield, and only provides helpful clues to an underlying inflammatory mucosal disorder such as eosinophilic esophagitis when presentation consists of dysphagia or food impaction, or when endoscopic findings of eosinophilic esophagitis are found.[22] Mucosal damage from reflux can lead to dilated intracellular spaces, but this requires advanced techniques such as electron microscopy for optimal characterization.[3,23]

When upper endoscopy is unrevealing, ambulatory reflux monitoring performed off PPI therapy can detect abnormal reflux

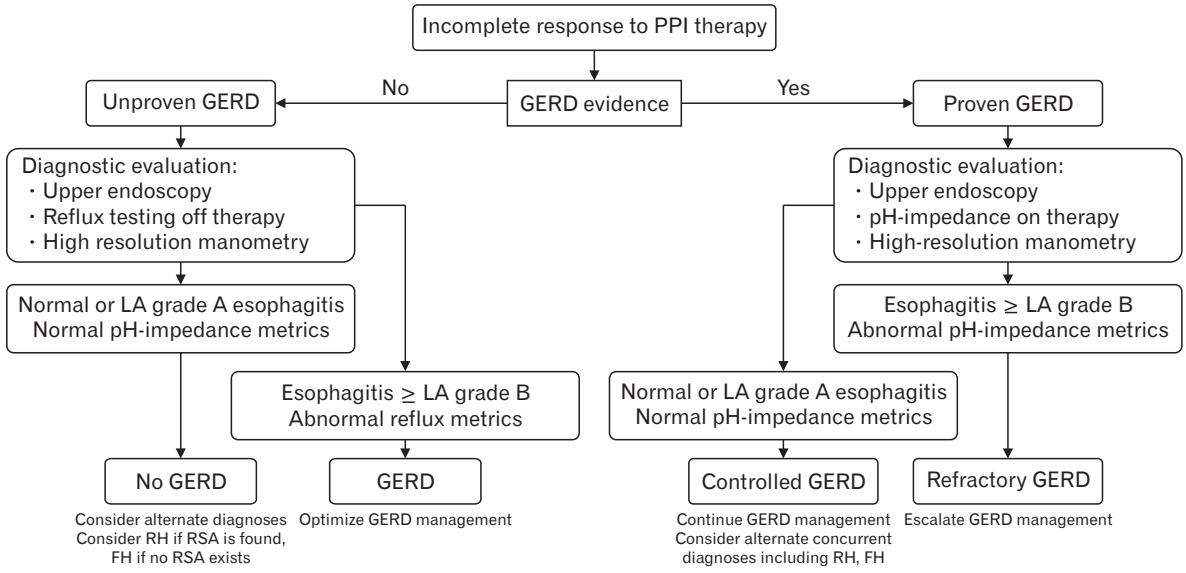

Figure 1. Algorithm for evaluation and management of esophageal symptoms suspicious for reflux disease. The concepts of proven gastroesophageal reflux disease (GERD) (prior objective evidence for GERD is present) and unproven GERD (no prior objective evidence for GERD) determine the optimal methodology of investigation of symptoms that persist despite proton pump inhibitor (PPI) therapy. The intent of evaluation of unproven GERD is to determine if GERD exists, while the intent in proven GERD is to determine if GERD persists despite therapy, which may need to be escalated if testing suggests persisting GERD evidence. LA, Los Angeles classification; RH, reflux hypersensitivity; RSA, reflux-symptom association; FH, functional heartburn.

burden to conclusively diagnose GERD. Although both pH and pH-impedance monitoring options provide accurate assessment of distal esophageal acid exposure and symptom correlation with reflux episodes, pH-impedance monitoring can distinguish weakly acidic from acidic reflux, provide an assessment of baseline mucosal impedance, and identify proximal extent of refluxate.[24] On the other hand, ambulatory (wireless) pH monitoring allows for up to 96 hours of pH monitoring, which can overcome day-to-day variation in reflux burden, and may guide PPI discontinuation if reflux is physiologic.[25] Moreover, the wireless pH probe can be placed during index endoscopy when no conclusive reflux changes are seen, if scheduled off PPI therapy. In contrast, catheter based pH and pH-impedance monitoring requires high-resolution manometry (HRM) to localize the lower esophageal sphincter (LES) for accurate positioning, and only provides a one-day assessment, which could be the patient's average day, best day, or worst day in terms of reflux burden.[26]

The primary metric assessed from reflux monitoring studies is acid exposure time (AET), the percent time distal esophageal pH is < 4.0 over the course of each day for wireless pH studies, or for the extent of the study for catheter based pH and pH-impedance studies.[3,16] Increasing AET correlates with increasing severity of esophagitis and increased length of intestinal metaplasia.[3,4,16] The role of weakly acidic refluxate in pathologic mucosal damage is less clear.[8,14] Reflux episodes on pH-impedance monitoring are identified according to the principles outlined by the Wingate consensus.[24] Interpretation of reflux monitoring data is based on criteria established by the recently updated Lyon consensus 2.0, with AET < 4%, total reflux episodes < 40 and/or mean nocturnal baseline impedance (MNBI) > 2500 ohms comprising physiologic acid burden within the "normal" spectrum.[27] At the opposite end of the spectrum, AET > 6% and total reflux episodes > 80 are considered conclusively abnormal.[3,24] When metrics are inconclusive (AET 4-6% and/or 40-80 total reflux episodes), adjunctive evidence such as low MNBI, reflux-symptom association and/or > 80 reflux episodes mark abnormal reflux burden and may sway the diagnosis toward conclusive GERD.[3,15,28,29]

Within the physiologic spectrum (AET < 4.0%), reflux-symptom association evaluation may allow further segregation of the symptomatic phenotype into reflux hypersensitivity (positive symptom association) or functional heartburn (negative reflux association); normal MNBI and postreflux swallow-induced peristaltic wave index are additional supportive evidence of these diagnoses.[18]

When considering alternative diagnoses in a patient with refractory symptoms, evaluation of esophageal motor function using HRM can be of value. Specifically, achalasia should be ruled out

since approximately 1% of preoperative HRM studies have been demonstrated to show evidence of achalasia spectrum disorders.[30] In addition to accurate localization of the LES for placement of pH or pH impedance catheters, HRM can detect pathophysiologic markers of GERD including suboptimal esophagogastric junction (EGJ) barrier function, abnormal EGJ morphology based on degree of separation between the LES and crural diaphragm, and compromised esophageal body peristaltic function.[15,31,32] Increasing prevalence of esophageal hypomotility (ineffective esophageal motility [IEM] and absent contractility) associate with increasing severity of GERD, hypothesized to be related to poor refluxate clearance, especially in the supine position.[15,30,31,33,34] Moreover, peristaltic integrity may have significance, with increasing length of esophageal body peristaltic breaks (fragmented and failed peristalsis) associating better with abnormal AET in comparison to weak swallows.[35]

Evaluation of Symptomatic Patients With Proven Gastroesophageal Reflux Disease

Suboptimal symptom control in patients with proven GERD despite optimized antisecretory therapy warrants further investigation aimed at determining whether refractory GERD symptoms are secondary to inadequate reflux control versus alternate non-GERD esophageal and/or non-esophageal disorders. Evaluation starts with an upper endoscopy, during which persisting EE (LA grade B or higher) or recurrent peptic stricture confirms refractory GERD, while LA grade A esophagitis is inconclusive requiring further supportive evidence. A significant proportion of patients with prior erosive disease will demonstrate mucosal healing on repeat upper endoscopy, which may limit the diagnostic utility of endoscopy.[8,21]

Reflux evaluation using pH-impedance monitoring while on optimized PPI therapy is the mainstay in diagnostic assessment when endoscopy is unrevealing, regardless of how GERD was initially confirmed. A lower AET threshold of 4% is adequate to affirm refractory GERD in this context; a finding of reflux episodes > 80 is supportive.[3,8,36,37] High proximal migration of refluxate has been demonstrated to associate with symptoms on pH-impedance monitoring; reflux symptom association with < 40 reflux episodes, or < 80 episodes without other supportive GERD evidence might suggest overlapping reflux hypersensitivity rather than refractory GERD.[38-40] If not previously performed, HRM can add pathophysiologic evidence supporting GERD. In patients with IEM, provocative testing using multiple rapid swallows assesses contraction reserve, which can be used to counsel patients regarding risk of postoperative dysphagia if antireflux surgery (ARS) is being considered.[3,8,31] Functional lumen imaging probe can assess integrity of secondary peristalsis but this has not been studied in the context of refractory GERD and further research is needed.

Conversely, when pH-impedance monitoring is abnormal and refractory GERD is diagnosed, the treatment plan should be re-evaluated and management should be optimized with the goal of better reflux control to improve symptoms and subsequently quality of life, and prevent GERD-related complications. When esophageal evaluation is negative, both esophageal DGBIs (such as reflux hypersensitivity and functional heartburn) and non-esophageal disorders (rumination, supragastric belching, laryngeal and pulmonary disorders, gastroparesis, and cardiac disease) need to be considered as potential mechanisms of symptom generation.

Management

An understanding of the mechanism of GERD refractoriness to existing treatment using clinical evaluation, upper endoscopy, and esophageal physiologic testing can help personalize further management. Nevertheless, approaches recommended for reflux symptoms at initial presentation also apply to refractory GERD, and these need to be implemented prior to escalation of management especially to non-reversible options (Fig. 2).

Lifestyle Measures

No matter the clinical presentation, lifestyle modifications should be incorporated into the management strategy of all patients with refractory GERD. Weight management is an important consideration for overall health, and is beneficial in improving both symptoms and acid burden.[41-45] Although weight loss may be achieved by the patient independently, a structured weight loss program may be more impactful in improving reflux symptoms, as demonstrated using validated reflux questionnaires following a 6-month weight loss program in overweight and obese individuals.[42] Although a graded response has been demonstrated between degree of body mass index decline and improvement of reflux symptoms, benefits specific to refractory GERD have not explicitly been reported.[44] Beyond weight loss, cessation of tobacco and alcohol use should be generally considered for overall health benefits.

Tobacco use has finite associations with GERD pathophysiology, demonstrated on meta-analysis of the significantly higher risk of GERD and associated symptoms in smokers compared to non-smokers.[45-47] In contrast, literature describing the role of alcohol use in GERD pathophysiology is mixed. Although alcohol can poten-

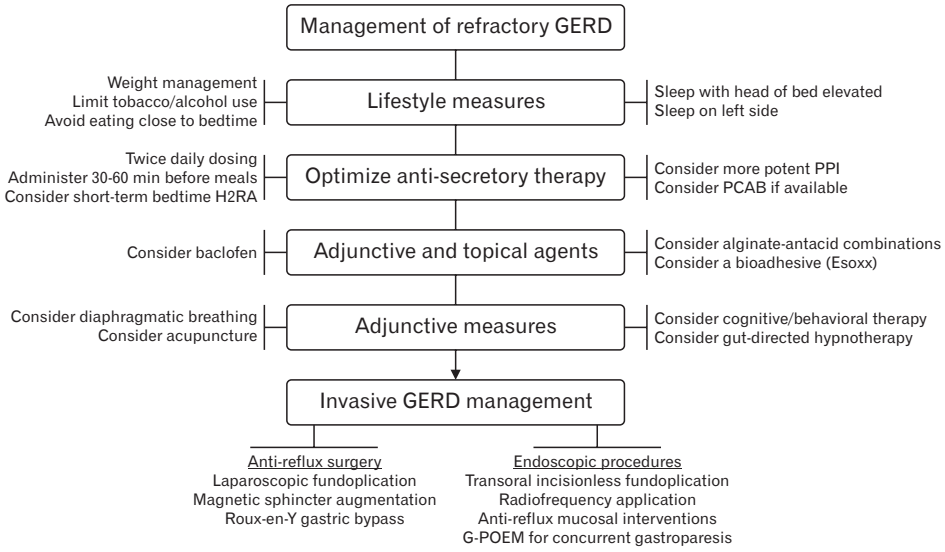

Figure 2. Management of refractory gastroesophageal reflux disease (GERD). Lifestyle adjustments are useful in any patient with reflux symptoms. Antisecretory therapy should be optimized and escalated if indicated. Adjunctive and topical agents, as well as adjunctive measures can be employed to improve symptoms. In patients with objective evidence of refractory GERD, escalation of management to anti-reflux surgery or other invasive interventions may be appropriate. H2RA, histamine H2 receptor antagonist; PPI, proton pump inhibitor; PCAB, potassium competitive acid blocker; G-POEM, gastric peroral endoscopic myotomy.

tially trigger esophageal symptoms in some patients and use should be limited accordingly, most studies suggest no significant cause-and-effect association.[46-48] There are no systematic studies defining complete dietary exclusion of food groups for symptom improvement, but avoidance of triggering foods and drinks should be individualized.[8,45,48] However, separating the last meal of the day from bedtime by several hours can reduce supine acid exposure, with available evidence demonstrating significant decrease in night-time acid burden with an earlier evening meal.[49] Additionally, supine acid exposure is lower with elevation of the head of the bed and sleeping in the left lateral decubitus position.[4,8,50-56]

Optimization of Anti-secretory Therapy

The efficacy of PPI therapy is dependent on the proportion of time intragastric pH is > 4.0 in the 24-hour period following administration, which is maximal if the PPI is taken the first meal of the day. When evaluating the effectiveness of a PPI regimen in patients with refractory GERD, it is critical to first confirm adherence.[57] An astonishing number of patients do not take their PPI as prescribed, with approximately one-half only using the medication on an intermittent basis.[58-60] For the most effective blockade of gastric acid secretion, optimal timing of PPI administration is 30-60 minutes before a meal.[8,61] The importance of a good history to confirm adherence and timing has been emphasized in prior studies that demonstrated as few as 10% were taking their PPI as prescribed.[58,62]

The benefit of PPI therapy can be further optimized by increasing dose frequency to twice daily, which can provide incremental symptom benefit, esophagitis healing, and lower acid burden compared to once-daily administration in refractory GERD.[63-65] There is no evidence that dosing more often than twice daily has additional benefit.[66] Inadequate symptom response or esophagitis healing despite optimized twice daily dosing for 4-8 weeks may require transition to a more potent PPI.[66,67] Although available literature is limited, some studies suggest differing omeprazole-equivalent potencies between PPIs while others support interchangeable use without difference in outcomes.[64,66,67] Moreover, when evaluating omeprazole-equivalent potencies, pantoprazole has lower potency, while esomeprazole, dexlansoprazole, and rabeprazole have higher potency compared to omeprazole; lansoprazole is mostly equivalent to omeprazole.[66]

Pharmacokinetics, particularly metabolism through the hepatic cytochrome P450 (CYP2C19) system is a consideration when deciding the optimal PPI regimen.[65,68,69] While twice daily PPI therapy appears to provide adequate symptomatic response in up to 90% of refractory GERD patients, rapid PPI metabolization has been identified as a risk factor for refractory GERD in some patients.[65,68-70] A higher prevalence of rapid metabolizers has been identified in Caucasian patients while African Americans are less likely to have CYP mutations associated with rapid metabolism.[71] Comparatively, patients of Asian descent are more likely to possess CYP mutations associated with normal, intermediate, and poor metabolism phenotypes.[72] Nevertheless, in patients at risk for rapid metabolizer status with an unsatisfactory response, a PPI that bypasses hepatic CYP metabolism such as esomeprazole and rabeprazole may be an option.[65,68,69] Although genotying of CYP metabolizer status is possible, this is not widely available and can add a

significant cost burden; thus, this is not typically recommended over switching to an alternate PPI.[73]

Other Acid Suppressants

Alternative classes of antisecretory medications may have benefit as adjunctive therapy in refractory GERD. Nocturnal acid breakthrough, defined as at least 1 overnight hour of intragastric pH < 4.0 despite optimal PPI therapy, can manifest as nighttime symptoms. Histamine H2 receptor antagonists (H2RAs) are sometimes utilized at bedtime, since histamine release can be a mechanism underlying nocturnal acid secretion,[71] and histamine blockade can provide symptom relief from reduced nocturnal acid breakthrough in the short term.[71,74-80] When effective, tachyphylaxis and medication tolerance can return nocturnal acid production to baseline levels within 1 week to 1 month despite continued use of the medication, limiting H2RA efficacy.[71,74-80] Patients with H2RA tachyphylaxis may ultimately benefit from as needed use rather than adherence to a fixed regimen.

PCABs are an emerging class of acid suppressants that are promising in the management of refractory GERD. Although similar to PPIs in that they both inhibit the gastric hydrogen-potassium ATPase, PCABs achieve acid suppression through a reversible potassium-competitive inhibition of the proton pump, resulting in faster, more potent acid control without need for pre-meal administration.[81] Multicenter randomized trials in Asia and North America have demonstrated non-inferiority of the PCABs vonoprazan, tegoprazan, and fexuprazan compared to traditional PPIs, with particular effectiveness in advanced grade esophagitis, including in rapid PPI metabolizers since PCABs are metabolized by a different CYP enzyme system (CYP 3A4).[82-84] Faster symptom benefit has also been demonstrated with PCABs, especially symptoms associated with acidic reflux.[85]

Reflux Inhibitors and Mucosal Protective Agents

Baclofen, a gamma aminobutyric acid-B (GABA-B) receptor agonist, can reduce frequency of transient LES relaxations (TLESRs). Since TLESRs are the primary mechanism of gastroesophageal reflux, baclofen has proven useful by reducing number and duration of reflux episodes that could be contributing to refractory symptoms.[8,86-88] Baclofen has been shown to be effective in reducing symptoms both with and without large hiatal hernias.[89] However, its use is limited by side effects including sedation, lightheadedness, central nervous system depression, and short half-life necessitating multiple daily doses for results.[86,88] Unfortunately, attempts at pharmacokinetic optimization of alternate GABA-B receptor-targeting agents have fallen short of expectations, and no reflux-specific GABA-B agonist is currently available.[90,91]

Mucosal protective agents, on the other hand, are useful adjuncts for managing breakthrough heartburn and regurgitation despite PPI therapy. These agents can form a raft or mechanical barrier at the interface between meal-stimulated gastric acid (the postprandial acid pocket) and the esophageal mucosa to provide symptomatic benefit in patients with refractory GERD, with a favorable side effect profile.[4,8,92-94] Specifically, antacid preparations combined with alginate (Gaviscon Advance), as well as a hyaluronic acid-chondroitin sulfate based bioadhesive formulation (Esoxx) demonstrated benefit when used as an adjunct to PPI therapy compared to placebo with or without PPI in multicenter randomized-controlled trials.[92-94] Although relief of persistent GERD symptoms has been demonstrated with the addition of mucosal protective agents, there is a paucity of literature detailing effect on objective reflux metrics through pH-impedance monitoring.

Invasive Anti-reflux Management

In patients with objective evidence of refractory GERD and persistent symptoms despite optimization of medical therapy, invasive surgical, or endoscopic anti-reflux interventions are options (Fig. 2). When conclusive GERD evidence exists, laparoscopic ARS has demonstrated long-term efficacy comparable to PPI therapy in several randomized trials.[95-97] This benefit extends to patients with refractory GERD despite optimized PPI therapy, where ARS may be superior to medical management in symptom relief.[97] Long-term monitoring demonstrates sustained benefit over follow-up as long as 17 years, with at least 60% of patients able to remain off antisecretory therapy.[98,99] However, some patients require re-intervention for recurrent GERD or fundoplication failure, and dysphagia as well as gas bloat syndrome remain problematic side effects in others. While postoperative obstructive symptoms may arise because of a mechanical post-operative complication, thorough preoperative evaluation including HRM may partially mitigate the risk by identifying patients as higher risk of postoperative dysphagia, such as pre-existing dysphagia or IEM without contraction reserve.[6,100-105] Although data are mixed, considering a partial wrap could reduce the likelihood of late postoperative dysphagia.[102-104] Roux-en-Y gastric bypass is an option as primary treatment for refractory GERD, for failed fundoplication, or for refractory GERD

following sleeve gastrectomy, especially for morbidly obese patients where morbidity is lower compared to ARS.[6,8,106,107]

An alternative minimally invasive surgical option is magnetic sphincter augmentation (MSA) where a bracelet of magnets encased in titanium is implanted around the EGJ.[108,109] As many as 58% normalize esophageal AET within 1 year after MSA, and > 90% are able to halve their use of antisecretory therapy.[109,110] Although MSA appears beneficial in all PPI-refractory GERD, regurgitation-predominant symptoms achieve particularly favorable results.[8,111-113] Number of total reflux episodes > 80 on preoperative pH-impedance monitoring despite optimized medical therapy predicts patient satisfaction and improved symptom scores following MSA.[113] Sustained symptom improvement has been demonstrated 5 years from implantation, with reduction in PPI use from 100% to 15.3%, and moderate-to-severe regurgitation symptoms from 57% to 1.2%.[114] Dysphagia post-MSA was typically mild, with resolution in most patients (89% at 1 year and 96% at 3 years), and the need for device explant was infrequent.[109-111,114]

Among endoscopic approaches, transoral incisionless fundoplication (TIF) 2.0 creates a 3 cm valve with a 270° circumferential wrap without need for laparoscopic surgery.[115-120] Although TIF has reported success despite presence of < 2 cm hiatal hernia, laparoscopic crural repair can be performed in conjunction with TIF when necessary.[115-120] Short-term benefits are well demonstrated over PPI therapy in randomized trials, particularly for regurgitation-predominant symptoms.[115,117-120] Even refractory atypical GERD symptoms may improve, with nearly three-fourths of patients off PPI therapy at 12-month follow-up.[116] Long-term efficacy data are mixed; one 10-year study reported > 90% of patients off PPI or on doses 50% lower than baseline, yet others have reported decreased effectiveness over time.[115,117-120] Radiofrequency application (RFA, also termed Stretta) to the EGJ attempts to improve EGJ barrier function while reducing TLESR frequency through altering esophageal nerve and muscle function, and potentially through reduction in sensation perception.[121-124] While generally safe, efficacy of RFA remains under debate.[121-126] Separate meta-analyses have reported unchanged LES pressures and inconsistent outcomes in regards to PPI discontinuation, improvement in quality of life, and esophageal AET normalization.[122,123,125,126]

A newer endoscopic technique termed antireflux mucosectomy creates scarring around the EGJ using crescentic or circumferential mucosal resection to reduce reflux burden.[120,127-129] In observational antireflux mucosectomy studies, improvement in reflux-related quality of life has been demonstrated.[128] Other antireflux mucosal interventions reduce reflux in a similar fashion, including antireflux band mucosectomy (ARBM) and antireflux mucosal ablation (ARMA) using argon plasma coagulation.[129,130] A pooled success rate of 73.8% has been reported over short-term follow up with antireflux mucosal interventions in a meta-analysis of uncontrolled trials.[129] Post-procedure dysphagia requiring dilation was reported by 10%, while perforation occurred in 2.2%.[129]

For the subset of refractory GERD patients where gastroparesis co-exists, improving gastric emptying can improve reflux symptoms. Medical management with prokinetics is typically utilized at the outset. Gastric per-oral endoscopic myotomy can be an option for persistent delay in gastric emptying, especially when this is believed to contribute to refractory GERD symptoms. A recent multicenter retrospective study of 20 lung transplant patients with concomitant GERD and gastroparesis demonstrated normalization of pH testing in 90% with improvement in gastric emptying and ability to wean off PPI therapy in 75%.[131]

Other Measures

Complementary approaches benefit some refractory GERD patients. Diaphragmatic breathing can increase LES pressure and reduce postprandial reflux episodes.[132] In a randomized trial of patients with NERD or healed esophagitis, diaphragmatic breathing reduced abnormal AET with improvement in quality of life scores.[133] Benefits may last for as long as 9 months, with sustained improvement in quality of life as well as PPI discontinuation.[133] Both acupuncture and hypnotherapy can improve symptom intensity, especially chest pain, in refractory GERD.[133,134] Heightened psychological stress, anxiety, and/or depression exacerbate refractory GERD symptoms in population-based studies, which may benefit from targeted therapy administered by a behavioral psychologist.[135]

Prognosis

Identification and management of refractory GERD can reduce likelihood of undesirable effects of longstanding abnormal acid exposure, including erosive esophagitis, peptic stricture, BE, and esophageal adenocarcinoma. Optimized antireflux pharmacotherapy has been shown to successfully heal esophagitis in 72-93% of patients, while ARS has demonstrated comparable long-term outcomes in randomized controlled trials.[4,95,96] Beyond damage to mucosal integrity, refractory GERD may exacerbate physical symptoms that can significantly impact health-related quality of life. Conversely, despite adequate endoscopic healing and alleviation of abnormal acid burden, symptoms can persist because of overlap-

ping alternative mechanisms of symptom generation such as reflux hypersensitivity or functional heartburn among others. Delineating refractory GERD symptoms from refractory GERD is essential, as the treatment paradigm relies on this differentiation to achieve optimal clinical outcomes. In general, pharmacologic, endoscopic, and surgical interventions for refractory GERD have benefits that outweigh risks in well-characterized GERD, and management needs to be personalized to each patient's unique presentation. Each therapeutic option has a risk-benefit profile that should be reviewed with the patient.

Conclusions

Persistent esophageal symptoms despite seemingly adequate acid suppressive therapy is the starting point for evaluation to determine if GERD evidence exists. Refractory GERD is diagnosed when abnormal reflux metrics persist on endoscopy and/or pH impedance monitoring performed on optimized GERD therapy in patients with previously proven GERD. While several non-pharmacologic, pharmacologic, endoscopic, and surgical interventions are available at the disposal of the clinician for effective treatment of refractory GERD, the management strategy should be personalized to each patient, taking into account underlying comorbidities, risk-benefit profile, and patient preference.

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