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POSITION PAPER

ESNM/ANMS consensus paper: Diagnosis and management of refractory gastro-esophageal reflux disease

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Abstract

Up to 40% of patients with symptoms suspicious of gastroesophageal reflux disease (GERD) do not respond completely to proton pump inhibitor (PPI) therapy. The term "refractory GERD" has been used loosely in the literature. A distinction should be made between refractory symptoms (ie, symptoms may or may not be GERD-related), refractory GERD symptoms (ie, persisting symptoms in patients with proven GERD, regardless of relationship to ongoing reflux), and refractory GERD (ie, objective evidence of GERD despite adequate medical management). The present ESNM/ANMS consensus paper proposes use the term "refractory GERD symptoms" only in patients with persisting symptoms and previously proven GERD by either endoscopy or esophageal pH monitoring. Even in this context, symptoms may or may not be reflux related. Objective evaluation, including endoscopy and esophageal physiologic testing, is requisite to provide insights into mechanisms of symptom generation and evidence of true refractory GERD. Some patients may have true ongoing refractory acid or weakly acidic reflux despite PPIs, while others have no evidence of ongoing reflux, and yet others have functional esophageal disorders (overlapping with proven GERD confirmed off therapy). In this context, attention should also be paid to supragastric belching and rumination syndrome, which may be important contributors to refractory symptoms.

KEYWORDS
Barrett's esophagus, esophagitis, gastroesophageal reflux, laparoscopic fundoplication, peptic stricture, pH-impedance monitoring, proton pump inhibitor

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1 | INTRODUCTION

As many as 40% of patients with gastroesophageal reflux disease (GERD) will experience persistent symptoms despite proton pump inhibitor (PPI) therapy. According to the Montreal Consensus, heartburn and regurgitation represent typical symptoms of GERD whereas non-cardiac chest pain and extraesophageal symptoms (ie, laryngeal or pulmonary complaints) represent atypical symptoms.[1] Generally, the presence of primary typical symptoms portends a more favorable outcome to escalation of antireflux management such as antireflux surgery,[2] suggesting that extraesophageal symptoms in particular may be manifestations of other non-GERD associated pathologies. In fact, large proportions of patients with PPI refractory symptoms do not demonstrate conclusive evidence of GERD on objective testing.[3,4] Thus, a distinction needs to be made between refractory reflux-like symptoms (ie, symptoms may or may not be GERD-related), refractory GERD symptoms (ie, persisting symptoms in patients with proven GERD, regardless of whether related or not related to ongoing reflux), and refractory GERD (persisting objective evidence of GERD despite adequate medical management). Prudent objective evaluation, including endoscopy and esophageal physiologic testing, can provide insights into mechanisms of symptom generation and evidence of persisting GERD (Figure 1).

Acid suppression with PPI therapy is the mainstay of management of well-characterized GERD.[5] Although PPIs have revolutionized the therapy of GERD, they have several therapeutic shortcomings: (1) they are acid labile molecules making enteric coating a necessity along with the associated slow absorption and onset of action, (2) it takes 3–5 days to achieve full, steady-state antisecretory effect, (3) there is significant inter-individual pharmacodynamic variability due to cytochrome P450 2C19 genetic polymorphism and the associated effects on pharmacokinetics, (4) there are differences in potency between PPIs that may impact symptom control, (5) nocturnal acid breakthrough is frequently observed, even with twice-daily administration, and (6) PPIs do not impact GERD mechanisms or frequency of reflux events.[6,7] Thus, PPI therapy has potential to be further optimized in refractory GERD but may need adjunctive approaches including antireflux surgery under certain circumstances (Figure 2).

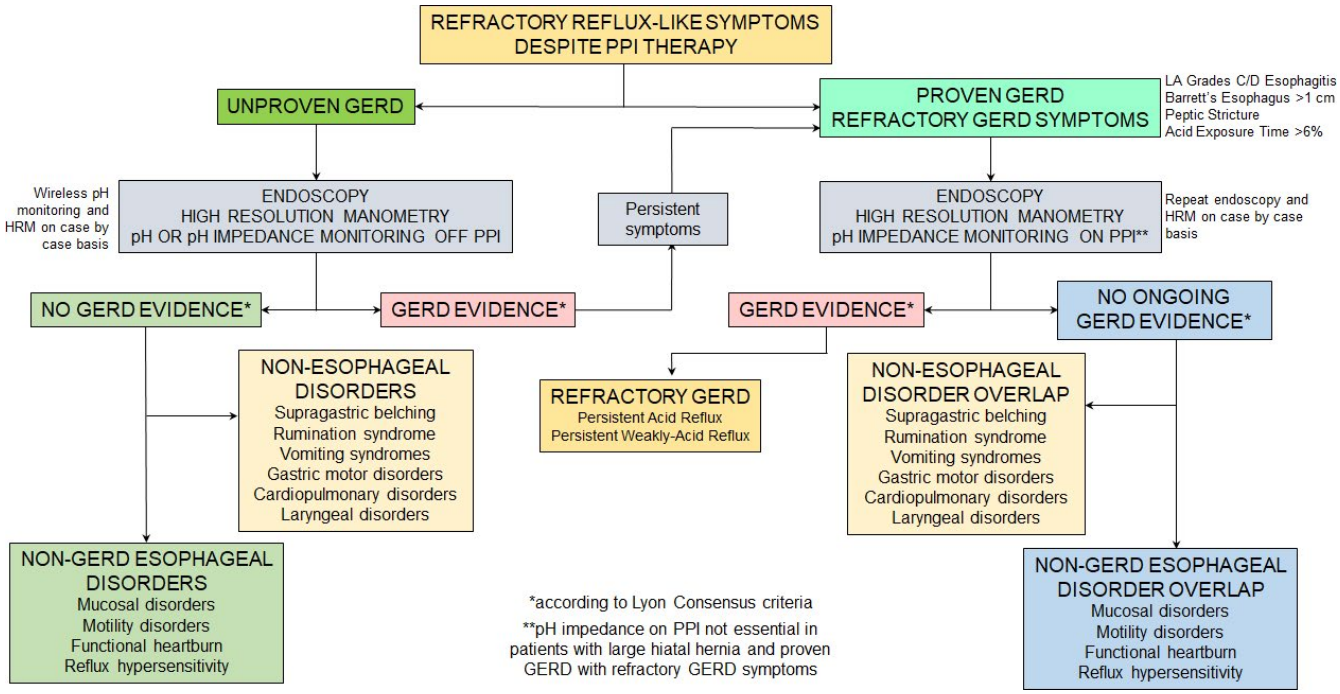

FIGURE 1 Algorithm for the diagnosis of refractory GERD. Patients with reflux symptoms despite PPI therapy should be investigated off PPIs if GERD has not been previously demonstrated. In addition to erosive esophagitis, endoscopy can identify mucosal disorders including eosinophilic esophagitis, pill esophagitis, and lichen planus. High-resolution manometry can diagnose achalasia spectrum disorders, and major motor disorders that can explain esophageal symptoms. In patients with esophageal symptoms, functional heartburn/chest pain is defined by normal acid exposure time (<4%) together with negative symptom association analysis; reflux hypersensitivity also has normal acid exposure time, but with positive symptom association analysis. Patients with proven GERD and persistent symptoms should be investigated on PPI therapy. Persistent acid reflux on PPIs is defined by the presence of grade B/C/D esophagitis, recurrent peptic stricture, acid exposure time >6%. Persistent weakly acidic reflux can be defined by more than 80 reflux episodes/24 h on pH-impedance monitoring and normal acid exposure time. In patients with proven GERD, hiatal hernia, and persistent regurgitation, pH-impedance monitoring is not mandatory since poorly controlled GERD is likely; only high-resolution manometry is needed to rule out major motor disorders. When acid exposure time and number of reflux episodes are normal, functional esophageal disorders overlapping with GERD are present (reflux hypersensitivity or functional heartburn). Supragastric belching and rumination should be ruled out if clinically suspected

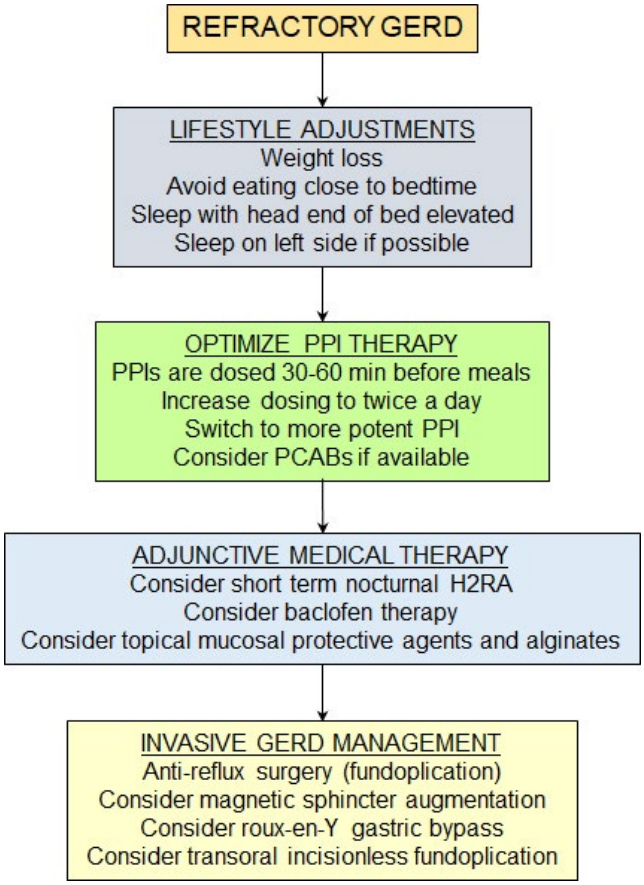

FIGURE 2 Management of refractory GERD. Once a diagnosis of refractory GERD is made, initial management can include lifestyle measures and optimization of PPI regimen. If symptoms persist, adjunctive medical therapy can be instituted, including short-term H2 receptor antagonists (H_2RA), baclofen, and mucosal protective agents such as Gaviscon with alginate and Esoxx. Prokinetic agents have no evidence for benefit in refractory GERD. Invasive management options include traditional laparoscopic antireflux surgery, and magnetic sphincter augmentation. Roux-en-Y gastric bypass can be considered for obese patients with refractory GERD. Endoscopic options include transoral incisionless fundoplication and radiofrequency energy delivery, both of which require extensive discussions with the patient regarding potential risks and expected benefit

This consensus guideline was jointly commissioned by the European Society for Neurogastroenterology and Motility (ESNM) and the American Neurogastroenterology and Motility Society (ANMS) to address clinically relevant issues relating to refractory GERD. The co-chairs (FZ, CPG) invited internationally renowned GERD experts to author statements concerning definition, epidemiology, pathophysiology, diagnosis, and management of refractory GERD, with supporting evidence. These statements were finalized by consensus, with all the authors approving the final statements presented below. This guideline expands on clinical data and expert review available since the Montreal consensus,[1] to include concepts described in the ROME IV document on functional esophageal disorders,[8] and the Lyon consensus establishing criteria for conclusive GERD.[9]

2 | DEFINITIONS

Statement 1: The term "refractory GERD symptoms" refers to the persistence of symptoms on therapy in patients with prior objective evidence of GERD (erosive esophagitis, peptic stricture, long segment Barrett's esophagus, or abnormal esophageal acid exposure on reflux monitoring performed off therapy). "Refractory GERD" is defined as persisting objective GERD evidence despite medical therapy (erosive esophagitis, or abnormal esophageal acid exposure and/or elevated numbers of reflux episodes on reflux monitoring performed on therapy).

GERD presents with a spectrum of typical (heartburn, regurgitation) and/or atypical (chest pain, cough, hoarseness, asthma, throat clearing, and others) symptoms, which we propose to be termed "refractory reflux-like symptoms" if persisting after initial therapeutic trials (Table 1). The term "refractory GERD" has been used loosely in the literature, both for patients with proven GERD (patients with erosive esophagitis and/or abnormal esophageal acid exposure on pH metry) and those never previously tested for GERD with either endoscopy or reflux monitoring. Consequently, the term "refractory GERD" has been applied to 2 different populations: a true "GERD" population, and a mixed population including GERD and conditions mimicking GERD. Thus, studies evaluating "refractory GERD" without objective documentation of the presence of GERD are difficult to interpret.[9] Among patients with refractory GERD symptoms, some will have true refractory GERD, and the two terms are not mutually exclusive. We propose that the term "refractory GERD symptoms" only be applied to patients with persisting symptoms on therapy in those with prior objective documentation of GERD,

TABLE 1 Definition and Epidemiology Of Refractory GERD

Statement 1: The term "refractory GERD symptoms" refers to the persistence of symptoms on therapy in patients with prior objective evidence of GERD (erosive esophagitis, peptic stricture, long segment Barrett's esophagus, or abnormal esophageal acid exposure on reflux monitoring performed off therapy). "Refractory GERD" is defined as persisting objective GERD evidence despite medical therapy (erosive esophagitis, or abnormal esophageal acid exposure and/or elevated numbers of reflux episodes on reflux monitoring performed on therapy).
Statement 2: Refractory GERD symptoms are partially responsive or non-responsive to a stable dose of a PPI during a treatment period of at least 8 weeks in patients with prior objective evidence of GERD.
Statement 3: Based on randomized trials, about a third of GERD patients receiving standard-dose PPI have inadequate symptom response at 8 weeks of treatment; inadequate endoscopic response (persistent erosions on endoscopy) despite standard-dose PPI is more prevalent with higher grades of esophagitis.
Statement 4: Refractory reflux-like symptoms affects all ethnicities with some predilection for Latino patients.
Statement 5: Refractory reflux-like symptoms are more likely to be reported by females, those with low BMI, with dyspepsia and/or IBS, with nighttime symptoms, and with sleep disturbances. Refractory GERD symptoms are not associated with presence or absence of *Helicobacter pylori*.

preferably off antireflux treatment. According to the Lyon consensus, objective evidence of GERD consists of Los Angeles grades C/D erosive esophagitis, peptic stricture, long segment Barrett's esophagus (BE) (>3 cm), or abnormal esophageal acid exposure time (AET) on pH metry (>6% for % total time pH <4).[9] However, persistence of LA grade B esophagitis on endoscopy performed on PPI therapy would be indicative of persisting or refractory GERD.[10,11] Further, recent data suggest that patients with regurgitation and >80 reflux episodes on MII-pH monitoring performed on PPI therapy demonstrate symptom improvement and satisfaction with invasive GERD management,[12] suggesting that this criterion may be an indicator of refractory GERD as proposed by the Lyon consensus.[9] Therefore, we propose that "refractory GERD" be applied to persistence of objective evidence of GERD (LA grades B/C/D esophagitis, abnormal AET, and/or elevated numbers of reflux episodes) despite adequate GERD management. This includes persistence of LA grade B esophagitis or higher on PPI therapy regardless of the fact that esophagitis may have improved from the initial "off PPI" LA grade.

Persistence of erosive esophagitis and/or abnormal esophageal acid exposure on pH metry (true refractory GERD) can be the cause of refractory GERD symptoms. However, overlap of GERD with reflux hypersensitivity, functional heartburn, or functional dyspepsia may also explain residual symptoms, in the absence of objective GERD evidence on PPI therapy.[4,13] Further, a cause-and-effect relationship may not always be demonstrable between persisting symptoms, especially extraesophageal symptoms and persisting objective GERD evidence despite PPI therapy. Disorders mimicking GERDs such as rumination, supragastric belching, eosinophilic esophagitis, and major esophageal motility disorders can also be responsible for lack of response to treatment.[14] Consequently, investigation is generally required to determine the underlying cause and to tailor treatment approaches in patients with refractory GERD symptoms.

Statement 2: Refractory GERD symptoms are defined as partially responsive or non-responsive to a stable dose of a PPI during a treatment period of at least 8 weeks in patients with prior objective evidence of GERD.

Treatment response in GERD patients varies with typical versus atypical symptoms, PPI type and dose, and duration of treatment among other factors. Currently approved PPI therapy for GERD consists of the standard dose of any available PPI, taken once daily before breakfast, although pharmacological differences in PPI potency may impact treatment response.[7] However, an increase in PPI dosing may improve response rates in some symptomatic GERD patients.[15] Furthermore, inhibition of gastric acid secretion is more profound on double-dose PPI compared to a single dose.[16] This is the rationale for the requirement of failure of double-dose PPI for a diagnosis of refractory GERD in clinical practice. Duration of PPI treatment needed for response may vary by symptom, with atypical symptoms requiring longer therapy than typical symptoms. No response or a partial response to PPI is reasonable as a qualifier for refractory symptoms; therefore, defining these terms is pivotal to proper diagnosis of refractory GERD. While definition of complete lack of response is obvious, partial response implies subjective decrease of symptoms, defined by frequency and severity of residual symptoms. Studies have typically defined partial response as a decrease of at least 50% in symptom frequency, severity, or both, using validated questionnaires (GERDQ, GERD-HRQL) and visual analog scales.[17–18] In clinical GERD management, a qualitative symptom management assessment may be adequate, and quantification using questionnaires may not be necessary. However, compliance with therapy may confound this definition. Indeed, in a large randomized US trial, 11% with persistent heartburn despite PPI therapy (of varying doses and duration) responded to a 2-week standardized regimen of omeprazole 20 mg bid, highlighting the importance of medication compliance in defining symptom relief.[3]

While we propose that refractory GERD should only be considered in clinical practice after failure of twice-daily PPI therapy, drug development trials for GERD typically utilize currently approved (once daily) PPI dosing as the comparison standard. Although this suggests a different refractory GERD definition for drug development, this dichotomy in definitions allows pharmaceutical companies to design studies within this area of unmet need that compare new products to currently available PPIs in doses approved by regulatory organizations.

3 | EPIDEMIOLOGY

Statement 3: Based on randomized trials, about a third of GERD patients receiving standard-dose PPI have inadequate symptom response at 8 weeks of treatment; inadequate endoscopic response (persistent erosions on endoscopy) despite standard-dose PPI is more prevalent with higher grades of esophagitis.

From 10% to 54% of patients with GERD symptoms fail to respond adequately, either partially or completely, to a standard-dose PPI (Table 1).[19–22] In observational primary care and community-based studies, persistent GERD symptoms were reported in 45% (30–60%) of study participants.[23] A systematic review reports higher rates of persistent troublesome symptoms in randomized trials [heartburn: 32% (25%–39%), regurgitation 28% (26%–30%)] compared to non-randomized trials [heartburn: 17% (6%–28%), regurgitation: 28% (26%–30%).[23] Among 3229 respondents to a US-based survey, 54% reported persistent GERD symptoms (heartburn or regurgitation) 2 or more days in the previous week while taking a daily PPI.[24] A higher prevalence of partial response has been reported with non-erosive reflux disease (NERD, 19.9%) compared to erosive esophagitis (14%).[25] Importantly, the authors have found that lack of response to PPI was uncommon, accounting for only 2.4% in NERD and 1.4% in erosive esophagitis.

The prevalence of persisting esophagitis depends on whether single-dose or double-dose PPI therapy was utilized. Using the typical pharma protocol of standard single-dose PPI, pivotal PPI treatment trials have demonstrated that severe grades of erosive esophagitis (using any endoscopic grading system) are associated with lower healing rates after 8 weeks. In one study, standard-dose lansoprazole and omeprazole resulted in persistent esophagitis rates

of 8% in LA grade A esophagitis, 15% in grade B, 20% in grade C, and 30% in grade D esophagitis.[10] Another study comparing 8-week therapy with standard-dose omeprazole (20 mg) to 40 mg esomeprazole documented failure rates of 9.6% and 6%, respectively, in LA grade A esophagitis, 28.7% and 10.6 in grade B, 29.6% and 12.8% in grade C, and 36.2% and 20%, respectively, in grade D esophagitis.[11] Duration of PPI therapy will also influence prevalence of persisting esophagitis, as longer PPI therapy could potentially allow more severe LA grades of esophagitis to heal. This is the basis for at least 12 weeks of adequate medical therapy before considering repeat EGD to document healing of esophagitis, especially in higher LA grades of esophagitis.

Statement 4: Refractory reflux-like symptoms affects all ethnicities with some predilection for Latino patients.

Although the definition of refractory GERD varies widely between publications, Asian studies report similar rates of partial or lack of response to PPI treatment as Western countries (6.6%–45%),[26–29] although most of these studies are symptom-based and do not report objective GERD evidence. While Caucasians demonstrate more esophageal inflammation and GERD-related complications than African Americans or Asians, a recent large population-based US study showed no difference in rates of PPI refractory symptoms among different ethnic groups exposed to similar environmental factors. However, Latino individuals were more likely to have persistent symptoms despite taking PPIs (OR 2.44, 95% CI 1.42–4.20).[24]

Genetics, pathophysiological, and physiological factors, environmental factors, and idiosyncratic reactions may all contribute to observed ethnic differences in response to medical GERD management.[30] Genetic differences in cytochrome P450 2C19 (CYP2C19), an important enzyme in PPI metabolism, may render some patients as poor metabolizers, and consequently, as better responders to PPIs. Studies have demonstrated that poor metabolizers based on CYP2C19 are more common among Asians (8%–20%), as compared to Caucasians/white (3%–5%) and African Americans/blacks (3%–5%).[30] Environmental factors such as lifestyle, type, and amount of food consumption, and BMI are also important in determining response to medical management, with a profound effect on the first generation of any ethnic group when emigrating to a different geographic region of the world.[31] Most studies in refractory GERD did not compare response to PPI treatment among the different ethnic groups.

Statement 5: Refractory reflux-like symptoms are more likely to be reported by females, those with low BMI, with dyspepsia and/or IBS, with nighttime symptoms, and with sleep disturbances. Refractory reflux-like symptoms are not associated with presence or absence of *Helicobacter pylori*.

Persistent reflux-like symptoms despite PPI treatment are more likely to be reported in studies with higher proportions of female participants (>60% vs <50%) with a risk ratio (RR) of 3.66 ($p < 0.001$).[23] Female patients also require higher PPI doses for symptom control.[25,31] In contrast, men have a higher likelihood of response to antireflux treatment.[32,33]

While obesity is a known association of abnormal esophageal reflux burden, low body mass index (BMI) has been demonstrated to associate with poor response to PPI therapy,[34–36] and both symptom response and esophageal healing improve as BMI increases,[35] regardless of erosive or non-erosive GERD. Although the underlying mechanism is unclear, this is likely related to the linear association between increasing BMI and higher esophageal acid exposure, and the fact that those with low BMI may either be predisposed to functional mechanisms or did not have conclusive GERD prior to PPI therapy. GERD with a concurrent functional gastrointestinal disorder such as functional dyspepsia or irritable bowel syndrome (IBS) is less likely to respond to PPI treatment compared to absence of a functional GI disorder.[36,37] Patients with GERD overlapping with functional gastrointestinal disorders perceive their symptoms to be more severe than those without such an overlap, suggesting that visceral hypersensitivity is a mechanism for this phenomenon.[20,37]

A Gallup Poll found that nighttime breakthrough symptoms were the most common presentation of refractory reflux symptoms. In a multicenter survey, nighttime symptoms were the most predictive of PPI refractory symptoms (OR = 2.56), followed by daytime sleepiness (OR = 1.64) and poor quality of sleep (OR = 1.67).[38] Lack of response or partial response to PPI treatment was associated with higher scores on the Pittsburgh Sleep Quality Index questionnaire, compared to PPI responders.[34,39]

Helicobacter pylori (*H. pylori*) infection improves inhibition of acid secretion by PPIs, with greater acid suppression in *H. pylori*-positive patients when compared with *H. pylori*-negative patients.[40] While a few studies demonstrated a significant increase in healing and symptom control in *H. pylori*-positive patients,[41] others demonstrated a limited or lack of increase in healing or symptom control compared to *H. pylori*-negative patients.[42–44] Maintenance studies in GERD patients indicate that *H. pylori* status does not determine the PPI dose needed to control symptoms or esophageal inflammation.[45,46] In addition, the background prevalence of *H. pylori* infection has been declining, further limiting its effect on PPI response.

4 | PATHOPHYSIOLOGY

Statement 6: Mechanical esophagogastric junction factors (significant hiatal hernia, obesity, transient LES relaxations) can contribute significantly to refractory GERD.

The antireflux barrier, consisting of the intrinsic lower esophageal sphincter (LES) and the crural diaphragm, provides defense against reflux of gastroduodenal contents into the esophagus (Table 2).[47] In those with continued symptoms despite therapy, reflux may occur via one or both of two mechanisms: (1) transient LES relaxations (TLESRs), especially with an intact hiatus, and (2) low LES basal pressure especially with a hiatal hernia. Persistently increased TLESR numbers despite PPI therapy is seen in refractory GERD patients with aerophagia.[48] Even though TLESRs are the most frequent mechanism for reflux in healthy subjects and in patients with persistent GERD,[49] drugs targeting TLESRs have suffered from limited

TABLE 2 Pathophysiology of refractory GERD

Statement 6: Mechanical esophagogastric junction factors (significant hiatal hernia, obesity, TLESRs) can contribute significantly to refractory GERD.
Statement 7: Suboptimal acid-suppressive therapy is an important pathophysiologic mechanism in refractory GERD.
Statement 8: Weakly acidic or weakly alkaline reflux may be clinically important in patients with refractory GERD symptoms.
Statement 9: Persistent mucosal microscopic damage (dilated intercellular spaces) is associated with persistent reflux on PPI therapy
Statement 10: Esophageal hypersensitivity may underlie persistent symptoms in patients with refractory GERD symptoms
Statement 11: In patients with proven GERD with significant regurgitation, rumination syndrome, supragastric belching, and delayed gastric emptying may be contributors to symptoms
Statement 12: Metabolic and genetic factors may alter response to PPI therapy.
Statement 13: Psychological factors (stress/depression/anxiety and hypervigilance) may play a role in persistent reflux symptoms.

benefit and significant adverse events.[50] A hypotensive LES allows intra-abdominal pressure to overcome LES pressure both during straining and during TLESRs. An important contributor to a hypotensive LES is a hiatal hernia, which disrupts the natural protective angle between the long axes of the esophagus and the stomach (angle of His) and increases the risk for erosive esophagitis[51] and BE.[52] Thus, transition from physiologic to pathologic reflux is the consequence of aberrancy in one or more defensive mechanism, the most common being TLESR and hiatal hernia. Consequently, a hiatal hernia may be responsible for continued symptoms, especially regurgitation, in patients with refractory GERD despite acid-suppressive therapy. Elevated intragastric pressure can contribute to reflux potential by promoting retrograde flow to the intrathoracic esophagus with lower resting intraluminal pressure.

The postprandial acid pocket is a layer of newly secreted gastric juice that resides above the ingested food bolus and is positioned just below the esophagogastric junction (EGJ) in normal postprandial conditions.[53] Studies have shown that the acid pocket extends more proximally in GERD and that the position of the acid pocket is altered in patients with hiatus hernia to promote acid reflux.[54] Whether refractory patients have a distinct pattern of acid pocket compared to PPI responders is unknown, and there is no published evidence showing relationship of acid pocket to refractory GERD.

Obesity is a major risk factor for GERD symptoms, erosive esophagitis, BE, and esophageal adenocarcinoma,[55,56] through increasing gastric pressure resulting in increasing TLESR[57] and overcoming the LES pressure gradient.[58] In patients with refractory GERD, obesity, particularly central obesity (measured by the waist to hip ratio), may be an important underlying mechanism for poor response to PPI therapy.[56] Weight reduction, especially waist circumference, is shown to improve GERD symptoms and reduce esophageal acid exposure[59] and is an important therapeutic recommendation for overweight or obese GERD patients. Although not directly demonstrated in the literature, patients with low BMI and refractory symptoms are more likely to have functional esophageal disorders and esophageal hypersensitivity, while overweight and obese patients probably have a higher likelihood of having true refractory persisting GERD. Therefore, the impact of BMI on PPI response is not always consistent, and low BMI has also been reported to be a risk factor for refractory symptoms.[34–36]

Statement 7: Suboptimal acid-suppressive therapy is an important pathophysiologic mechanism in refractory GERD.

Gastric acid secretion is not elevated in GERD, including in patients with symptoms refractory to a PPI trial. In fact, the majority of patients with suboptimal acid suppression do not take their PPI appropriately before meals,[60] and confirming compliance to therapy is an important first step. The duration of time gastric pH is >4.0 positively impacts healing of esophagitis, which is achieved better with PPIs than with H2 receptor antagonists or with antacids, and with higher PPI dose compared to lower dose.[61,62] In patients taking their PPI appropriately, refractory GERD symptoms (esophageal or extraesophageal) may result from continued acid reflux in about 20%–30% on once-daily PPI therapy, decreasing to 5%–10% on twice-daily PPIs.[63] Therefore, in patients with continued symptoms on once-daily PPI therapy, increasing to twice-daily dosing may augment acid reflux control. Available data do not support increasing PPI dosing higher than double-dose daily, and addition of bedtime H2-receptor antagonist therapy to decrease nocturnal acid breakthrough does not provide sustained benefit.[64,65]

Statement 8: Weakly acidic or weakly alkaline reflux may be clinically important in patients with refractory GERD symptoms.

Refractory GERD symptoms, particularly regurgitation that persists despite acid suppression, may be associated with weakly acidic reflux in up to 36% of patients.[66–68] Two multivariate analyses posited that mixed liquid-gas reflux episodes with high proximal extent significantly associate with symptoms regardless of pH.[67,69] While weakly acidic and non-acid reflux may cause symptoms from esophageal distension[70] or gastroduodenal contents in the proximal esophagus,[67,71] a direct relationship to esophageal mucosal damage is questionable.[72,73] Presence or absence of symptom-reflux association with weakly acidic or weakly alkaline reflux may imply overlap with reflux hypersensitivity or functional heartburn, respectively (see Statement 22).[8] Besides weakly acidic or weakly alkaline reflux, bile reflux may play a role in refractory reflux symptoms. A recent phase 2b study of a bile sequestrant in refractory GERD despite once-daily PPI therapy has shown promise in reducing symptoms of heartburn and regurgitation,[74] lending credence to the role of gastroduodenal contents (potentially bile reflux) in symptoms, particularly regurgitation, that persist despite PPIs.

Statement 9: Persistent mucosal microscopic damage (dilated intercellular spaces) is associated with persistent reflux on PPI therapy.

Reflux of gastric contents of pH 5–6 containing bile acids may contribute to persistent symptoms despite PPI therapy. Dilated intercellular spaces (DIS) may be a marker of continued epithelial exposure to noxious gastroduodenal contents in patients

with refractory symptoms and NERD.[75] Animal and human studies show that esophageal mucosal integrity can be compromised when exposed to acid and weakly acidic content with bile acids,[76] which is reversible with appropriate therapy.[77] Intercellular spaces are widened in refractory heartburn patients with GERD on PPIs, but not in patients without pathological reflux.[78] Due to the patchy nature of DIS, alternate metrics that evaluate mucosal integrity include mean nocturnal baseline impedance (MNBI) on ambulatory pH-impedance studies,[79] and mucosal integrity (MI) using a balloon mounted impedance array during endoscopy.[80] More recently, baseline impedance using esophageal pH-impedance monitoring or a dedicated through-the-scope catheter has been validated as a marker of esophageal mucosal integrity or lack thereof.[80–82] Neither technique has been extensively studied in refractory GERD, but these approaches may uniquely identify those in need of escalation of therapy if altered epithelial integrity can be linked to reflux of gastroduodenal contents.

Statement 10: Esophageal hypersensitivity may underlie persistent symptoms in patients with refractory GERD symptoms.

Patients with persistent symptoms of reflux and normal upper endoscopy may have normal esophageal acid exposure but a strong association between physiologic acid or weakly acidic reflux events and symptoms,[83] including when pH-impedance monitoring is performed on PPI therapy in proven GERD. According to the Rome IV consensus, these patients are now categorized as having either conventional or overlap reflux hypersensitivity,[8] with visceral hypersensitivity as the proposed underlying mechanism. It is not known whether patients with reflux symptoms refractory to PPI have more severe visceral hypersensitivity than those who respond to therapy. However, patients with NERD and functional heartburn are demonstrated to be more sensitive to intra-esophageal acid challenge, balloon distension, and thermal or electrical stimulation compared to patients with erosive disease or controls.[84,85]

The mechanism of esophageal hypersensitivity is not completely clear but may involve DIS and exposure of mucosal nerves to acid, among other potential mechanisms.[86] Decreased resistance to transmucosal passage of refluxate components through DIS is one potential peripheral mechanism, demonstrated in vitro by measuring transmucosal resistance or flux of molecules across the mucosa of esophageal endoscopic biopsies mounted on Ussing chambers. A morphologic correlate is DIS, which can be identified on histopathology or, more accurately, on electron microscopy of esophageal biopsies.[75,81,87] Increased mucosal permeability (or decreased baseline impedance) has been demonstrated in studies evaluating NERD and reflux hypersensitivity, but not in functional heartburn.[82]

Patients with NERD have been shown to have more superficial mucosal nerves compared to other GERD phenotypes.[88] Studies have demonstrated that the transient receptor potential vanilloid 1 (TRPV-1), a non-selective cation channel expressed by epithelial cells and sensory nerves, is present in healthy esophageal mucosa but up-regulated in patients with erosive esophagitis and NERD.[84] Luminal contact with neural and epithelial-sensitive receptors leads to sensitization of peripheral afferent nerves (peripheral sensitization) and sensitization of spinal dorsal horn neurons (central sensitization).[89] Once central sensitization is established, it can continue to potentiate pain after the initiating peripheral stimulus is discontinued.

Inflammatory mediator-induced reduction in the transduction threshold of nociceptor primary afferents is believed to cause pain hypersensitivity at the site of injury or inflammation, resulting in a heightened awareness of subsequent painful stimuli (*primary hyperalgesia*), and the perception of innocuous stimuli as being painful. In patients with NERD, increased areas of visceral (upper esophagus or stomach) and somatic hyperalgesia (chest wall) have been demonstrated[90] suggesting that central sensitization plays an important role. Acute stressors exacerbate heartburn symptoms in GERD patients by enhancing the perceptual response to esophageal acid exposure or acid perfusion.[91] Stress is often presumed to alter central processing of afferent signals, such as heartburn, but animal studies show that acute stress leads to DIS, which could also account for the increased sensitivity to reflux.[92]

As in patients with inflammatory bowel disease or irritable bowel syndrome, esophageal hypersensitivity can be present in other GERD phenotypes, including functional heartburn.[93] Increased esophageal sensitivity to chemical, mechanical, and electrical stimuli has been reported in functional heartburn,[83,94,95] but superficial mucosal nerves as seen in NERD have not been demonstrated.[96] Furthermore, up to 30% of patients refractory to PPI treatment diagnosed as reflux hypersensitivity can have superimposed behavioral disorders, such as increased supragastric belching or rumination.[97]

Statement 11: In patients with proven GERD with significant regurgitation, rumination syndrome, supragastric belching, and delayed gastric emptying may be contributors to symptoms.

Although many patients with GERD have abnormal gastric emptying and dyspepsia, it is difficult to prove a cause-and-effect link to PPI refractoriness. The severity of reflux symptoms in patients carrying a diagnosis of gastroparesis correlates with the gastroparesis symptom index, but correlations with gastric retention and esophageal pH monitoring are weak to non-existent.[98,99] On the other hand, delayed gastric emptying does provoke more reflux events with high proximal extent, which are known to have greater perception by GERD patients.[100]

A significant proportion of patients with refractory GERD symptoms are diagnosed with reflux hypersensitivity or functional heartburn following physiologic testing.[8] Many of these patients often describe typical reflux symptoms (heartburn or regurgitation) rather than belching despite supragastric belching being the initial mechanism of a symptomatic reflux event.[101,102] In fact, supragastric belching may be a hidden culprit of PPI refractoriness, particularly in patients with NERD and reflux hypersensitivity. Furthermore, a significant proportion of PPI refractory patients with predominant postprandial regurgitation may have rumination or supragastric belching,[14,101,103] accounting for almost half of these patients in a recent study.[97] This is clinically relevant, because supragastric belching and rumination do not respond to PPIs or pain modulators and require behavioral therapeutic approaches.[104,105]

Statement 12: Metabolic and genetic factors may alter response to PPI therapy.

Once non-adherence has been ruled out, ineffective control of acid secretion may be explained on the basis of differences in PPI metabolism.[106] A "rapid" PPI metabolizer might not achieve high enough serum PPI levels for adequate acid suppression.[107] Most studies examining the influence of CYP2C19 polymorphism on PPI therapy have had small sample sizes in single-center studies and have used relatively low PPI dosages. A recent meta-analysis from Japan concluded that the CYP2C19 rapid metabolizer genotype is a risk factor for PPI refractoriness in GERD patients with esophagitis.[108] Extensive metabolizers with erosive esophagitis have lower plasma PPI levels, lower rates of endoscopic healing, remission, and symptom response when treated with CYP2C19-dependent PPIs.[109] Assessing rapid metabolizer genotype or switching to a CYP2C19 independent PPI may be reasonable for optimization of acid suppression when PPI non-response is associated with persistent pathologic acid exposure, particularly in populations with a higher prevalence of extensive metabolizers, which is more common among Caucasians (59.7%–69.9%) as compared to Asian populations (27.7%–41.6%).[106] When symptom response to low-dose PPI was analyzed in erosive esophagitis and NERD patients based on the CYP2C19 genotype, esophagitis subjects with the CYP2C19 rapid metabolizer genotype had significantly higher symptom scores than other CYP2C19 genotypes. In contrast, the symptom scores of the NERD subjects with the CYP2C19 rapid metabolizer genotype were significantly lower than the scores of the subjects with the other CYP2C19 genotypes, suggesting that the impact of CYP phenotype in NERD is less relevant.[110] Consequently, the impact of CYP genotypes on PPI response in NERD is not well described[109] and could be further impacted by differences in relative potency of individual PPIs.[7]

Statement 13: Psychological factors (stress/depression/anxiety and hypervigilance) may play a role in persistent reflux symptoms.

Population-based studies have demonstrated that anxiety and depression increase reflux symptoms.[111] Despite similar reflux parameters on testing, GERD patients with depression, and especially anxiety, have greater effects of symptoms and lower quality of life, compared to GERD patients without these comorbidities.[112] Additionally, patients who respond suboptimally to PPI treatment are more likely to experience psychological distress.[37] Furthermore, heartburn may be either triggered by or worsened during life stress events, and psychological stress is associated with increased perception of esophageal stimuli.[113] Esophageal hypervigilance can be an important component of a learned behavior involving hyperawareness and early cue detection of future esophageal discomfort. Hypervigilance has been proposed as an important psychological mechanism in patients' refractory to PPI treatment.[114–116]

Patients with GERD have higher sensitivity to perfused acid after sleep deprivation compared with restful sleep,[117] and anxiety induction increases acid-induced esophageal hyperalgesia.[118] Psychological stress can exacerbate esophageal pain sensitivity by enhancing both peripheral and central mechanisms. Stress alters brain processing of sensation (as demonstrated by functional MRI studies) and may also alter the descending inhibitory and/or excitatory pathways that modulate spinal transmission of nociceptive signals. Acute psychological stress has important effects on autonomic nervous activity and on hypothalamic-pituitary-adrenal axis response (particularly with regard to corticotropin-releasing hormone-induced cortisol release).[119] Finally, studies in rats have shown that acute stress can induce DIS in esophageal mucosa. This was associated with increased mucosal permeability to small molecules and increased number of submucosal mast cells.[92] Therefore, psychological stress may contribute to esophageal hypersensitivity not only by central neural mechanisms and hypervigilance but also by stress-induced impairment of esophageal mucosal integrity.

5 | DIAGNOSIS

5.1 | Clinical features

Statement 14: In patients with proven GERD, both persistent typical symptoms and persistent atypical symptoms (non-cardiac chest pain, extraesophageal symptoms) on PPI therapy deserve further investigation to evaluate for poorly controlled GERD, functional esophageal disorders, motility disorders, and specific pulmonary or pharyngo-laryngeal etiologies as appropriate.

While persistent symptoms of heartburn or non-cardiac chest pain may represent poorly controlled GERD, they are often due to an overlap with a functional esophageal disorder through mechanisms of visceral hypersensitivity and hypervigilance (Table 3).[8] Functional heartburn, functional chest pain, or reflux hypersensitivity explain persistent symptoms in up to 75% of patients with GERD.[13,14,93] As many as 15% of patients with non-cardiac chest pain may have a major esophageal motility disorder such as achalasia, hypercontractile esophagus, or distal esophageal spasm on esophageal manometry.[120] Hence, evaluation for motility disorders is also warranted.[8]

In patients with proven GERD and persistent extraesophageal symptoms, associated conditions such as sino-pulmonary or laryngeal processes could be triggering symptoms independent of GERD. In a retrospective study of 115 patients with GERD undergoing antireflux surgery, the presence of primary extraesophageal symptoms was associated with an increased risk of postoperative symptom recurrence (adjusted hazard ratio 2.34; 95% CI 1.31, 4.17).[121] In 78 patients with extraesophageal symptoms, 45% with pathologic acidic and/or non-acidic GERD on multichannel intraluminal impedance pH (MII-pH) monitoring had significant physiologic and symptom improvement from laparoscopic Nissen fundoplication [122] indicating that MII-pH can identify patients who respond to escalation of GERD management. These findings underscore the importance of excluding non-GERD etiologies for ongoing symptoms. In particular, on therapy MII-pH is recommended for patients with proven GERD and persistent extraesophageal symptoms such as cough and

TABLE 3 Diagnosis of refractory GERD

Clinical features
Statement 14: In patients with proven GERD, both persistent typical symptoms and persistent atypical symptoms (non-cardiac chest pain, extraesophageal symptoms) on PPI therapy deserve further investigation to evaluate for poorly controlled GERD, functional esophageal disorders, motility disorders, and specific pulmonary or pharyngo-laryngeal etiologies as appropriate.
Statement 15: In patients with proven GERD and a large hiatal hernia, persistent regurgitation on PPI therapy is likely to be related to refractory GERD.
Endoscopy
Statement 16: Los Angeles Grade B/C/D esophagitis on endoscopy despite optimized PPI therapy is indicative of refractory GERD.
Statement 17: In patients with refractory GERD symptoms, non-specific inflammation on esophageal biopsies is not relevant, and the diagnostic yield of eosinophilic esophagitis is very low in the absence of dysphagia and specific endoscopic signs. Barrett's mucosa of any length is not indicative of poor GERD control.
Statement 18: Endoscopic and/or radiologic evaluation of EGJ morphology should be performed in patients with refractory GERD symptoms.
Statement 19: Recurrent esophageal peptic stricture despite optimized PPI therapy and/or dilatation is indicative of refractory GERD.
Physiologic investigations
Statement 20: Patients with persistent esophageal and/or extraesophageal symptoms on PPI therapy and no previously documented GERD should be investigated with endoscopy and ambulatory pH or pH-impedance monitoring off therapy to document presence or absence of baseline abnormal reflux
Statement 21: In patients with proven GERD and persistent symptoms on PPI therapy, esophageal manometry and 24-h pH-impedance on therapy are requisite to distinguish refractory GERD from functional esophageal disorders.
Statement 22: Overlap may be demonstrated between proven GERD (as evidenced by prior abnormal AET off PPIs and/or significant esophagitis), and reflux hypersensitivity or functional heartburn, when pH-impedance monitoring is performed on PPI therapy
Statement 23: In patients with inconclusive "of PPI" pH-impedance findings, other impedance parameters, including symptom association probability, post-reflux swallow-induced peristaltic wave (PSPW) index, and mean nocturnal baseline impedance (MNBI), may help identify patients with refractory GERD
Statement 24: Esophageal motility should be assessed using high-resolution manometry in patients with refractory GERD symptoms. High-resolution manometry can rule out major esophageal motility disorders and demonstrate esophagogastric junction and esophageal body motor abnormalities associated with GERD.
Statement 25: When rumination is suspected in patients with persistent regurgitation on PPI therapy, manometry with impedance, ambulatory, or stationary (postprandial), is indicated to distinguish rumination from GERD.
Statement 26: In asymptomatic patients with untreated Barrett's esophagus, testing for persisting reflux on PPIs is not recommended

laryngeal symptoms as esophago-pharyngeal reflux is often weakly acidic, and high acid exposure is uncommon in these patients.[123,124]

Statement 15: In patients with proven GERD and a large hiatal hernia, persistent regurgitation on PPI therapy is likely to be related to refractory GERD.

Refractory GERD symptoms can be both typical (ie, heartburn and regurgitation) and/or atypical (chest pain, laryngo-pharyngeal, pulmonary), but the probability that poorly controlled GERD is the underlying cause of atypical symptoms is much lower compared to typical symptoms. Persistent regurgitation tends to have a more favorable outcome to antireflux surgery compared to atypical reflux symptoms and even typical heartburn.[12,125,126] Regurgitation is perceived in response to luminal distension from retrograde gastroesophageal flow of refluxate or foul taste of the regurgitant and is a primary symptom when the antireflux barrier is disrupted, with a hiatal hernia or a hypotensive lower esophageal sphincter (LES). Further, hiatal hernia size is associated with greater GERD severity.[127,128] Therefore, persisting regurgitation despite PPI therapy in the setting of proven GERD and a large hiatus hernia is consistent with refractory GERD.

6 | ENDOSCOPY

Statement 16: Los Angeles Grade B/C/D esophagitis on endoscopy despite optimized PPI therapy is indicative of refractory GERD.

Although upper gastrointestinal endoscopy is recommended in patients with refractory reflux symptoms, the diagnostic yield is low because PPIs typically heal esophageal lesions that may have been initially present. The likelihood of persistent esophagitis in symptomatic patients despite PPI is 20%–30% after 4 weeks of therapy,[129] and 6.7% after 8 weeks.[130] Despite elevated acid exposure and/or positive symptom index, 71.4% of 35 patients with refractory GERD on PPIs had no evidence of esophagitis at endoscopy.[116] In fact, the absence of esophagitis remains associated with PPI refractoriness in patients with proven GERD and refractory symptoms.[67] Since most patients with refractory symptoms and proven GERD have a normal endoscopy, the presence of mucosal breaks despite PPI therapy may reflect poorly controlled acid reflux. Even though the Lyon GERD consensus proposed only grade C and D esophagitis as reliable for the conclusive diagnosis of GERD,[9] persistent grade B esophagitis after at least 8 weeks of PPI therapy should be considered as an indirect sign of refractory GERD.

Statement 17: In patients with refractory GERD symptoms, non-specific inflammation on esophageal biopsies is not relevant, and the diagnostic yield of eosinophilic esophagitis is very low in the absence of dysphagia and specific endoscopic signs. Barrett's mucosa of any length is not indicative of poor GERD control.

Gastroesophageal reflux has been associated with histological lesions such as increased epithelial thickness, basal cell hyperplasia, papillary elongation, increased intraepithelial eosinophil, neutrophil and mononuclear cell inflammation, erosions, and DIS.[132] While these histological lesions may help to differentiate patients with GERD from those with functional esophageal disorders[132–135] and microscopic esophagitis has been suggested by the Lyon consensus to be an adjunctive diagnostic tool in patients with inconclusive GERD testing,[9] there are no available data to suggest that microscopic inflammation reflects persistent pathological GERD in patients with proven GERD and refractory symptoms, although the converse is generally true, that is, FH patients rarely have microscopic inflammation.

Relationships between GERD and esophageal eosinophilia are complex, since 30 to 50% of patients with typical symptoms and endoscopic signs of eosinophilic esophagitis (EoE) will achieve clinical and histological remission after a 8-week course of PPI therapy.[136,137] The Rome IV criteria for functional esophageal disorders require both GERD and EoE to be ruled out and therefore recommends esophageal biopsies.[8] However, only 0.9 to 4% of patients with refractory heartburn and regurgitation prove to have EoE,[130,138,139] and the diagnostic yield is likely much lower in proven GERD patients with refractory symptoms despite PPI in the absence of dysphagia and endoscopic EoE features. Nevertheless, in this specific clinical situation, although not mandatory, biopsies are a simple complement to endoscopic esophageal inspection and should be performed when EoE remains in the differential diagnosis.

The diagnosis of BE, a consequence of long-standing GERD, requires esophageal biopsies demonstrating intestinal metaplasia. While long-term PPI therapy may reduce the risk of neoplastic progression of BE, it does not result in a complete normalization of esophageal mucosa.[140] Therefore, in a patient with refractory GERD symptoms, the persistence of BE at endoscopy cannot be, per se, indicative of poorly controlled GERD.

Statement 18: Endoscopic and/or radiologic evaluation of EGJ morphology should be performed in patients with refractory GERD symptoms.

The presence of a hiatal hernia associates with more severe reflux, esophageal mucosal lesions, and decreased PPI efficacy[141,142] with a linear association between hiatus hernia size and GERD severity.[127,128] Using landmarks validated by the Prague classification,[143] a sliding hiatal hernia can be diagnosed when the diaphragmatic hiatus is located ≥2 cm distal to the Z line. The EGJ can also be evaluated during retroflexion to determine the integrity of the EGJ,[144] with an abnormal flap valve associated with poor PPI response.[145] Although relatively subjective and confounded by presence of Barrett's mucosa, endoscopic assessment of EGJ morphology can be reliable in the diagnosis of large hiatal hernias >3 cm in size[146]; barium radiography is similarly reliable.[147] Both endoscopy and barium radiography have been shown to be less sensitive and specific compared to high-resolution manometry (HRM) for the diagnosis of hiatal hernia.[147,148]

Statement 19: Recurrent esophageal peptic stricture despite optimized PPI therapy and/or dilatation is indicative of refractory GERD.

The persistence or recurrence of peptic strictures on PPI therapy is likely indicative of poorly controlled GERD, although only indirect evidence is available in the literature. Several studies, including two randomized studies, have demonstrated the superiority of PPIs over H2 receptor antagonists (H_2RA) in preventing stricture recurrence after dilation.[149–152] Persistent heartburn after esophageal dilation has been shown to be a strong predictor of stricture recurrence.[153] Although no study has evaluated acid reflux control on PPIs in patients with recurrent peptic strictures, available evidence suggests that less effective control of acid secretion, and therefore acid reflux, is probably responsible for peptic stricture recurrence or resistance to medical therapy.

7 | PHYSIOLOGIC INVESTIGATIONS

Statement 20: Patients with persistent esophageal and/or extraesophageal symptoms on PPI therapy and no previously documented GERD should be investigated with endoscopy and ambulatory pH or pH-impedance monitoring off therapy to document presence or absence of baseline abnormal reflux.

The PPI trial has suboptimal sensitivity (71%) and specificity (44%) compared to endoscopy and reflux monitoring in confirming GERD,[9] and an estimated 17%–45% of patients remain symptomatic during antisecretory treatment despite a GERD diagnosis.[23] Under these circumstances, objective testing documents the presence or absence of baseline abnormal reflux. EGD rules out conditions such as EoE, drug-induced and infectious esophagitis, peptic stricture, neoplasia that can explain persistent symptoms but has low sensitivity in diagnosing GERD, especially in patients taking PPIs. If EGD is normal, ambulatory pH or MII-pH monitoring is the gold standard for establishing a GERD diagnosis and should be performed off PPI to identify baseline pathological acid exposure[9]. Use of prolonged wireless pH monitoring in this context has recently been demonstrated in a randomized blinded study to segregate PPI non-responders who can discontinue PPI use (associated with physiologic acid exposure) from those who need ongoing PPI therapy (associated with pathologic acid exposure).[154]

Why reflux events cause heartburn in some patients and chest pain in others is unknown. Among various etiologies of non-cardiac chest pain, GERD accounts 30 to 60% of cases, with functional esophageal disorders and esophageal motility disorders accounting for most of the remainder. Reflux episodes associated with chest pain are often acidic episodes that reach a higher proximal extent, with longer volume clearance time and acid contact

time.[155] Consequently, as many as 75% of non-cardiac chest pain patients with proven GERD achieve symptomatic improvement on PPIs.[156–158]

Management of extraesophageal symptoms is challenging and complicated by the fact that the laryngoscopic signs linked to GERD are not reliable because of intra-observer variation, low inter-observer concordance, and presence in as many as 86% of healthy individuals.[159,160] Even if GERD is present, a cause-and-effect relationship with extraesophageal symptoms is difficult to demonstrate, especially in the absence of PPI response. Therefore, in the absence of prior GERD evidence, esophageal reflux monitoring is performed off PPI therapy.

AET represents the most reproducible and reliable parameter for the diagnosis of pathological GERD, mainly because it is a continuous metric, which proportionally correlates with the severity of reflux. The Lyon Consensus considered an AET cutoff value of <4% as definitively normal and >6% as clearly pathological.[9] Number of reflux episodes is considered normal when <40 over 24 hours and abnormal when >80.[12] Abnormal numbers of reflux episodes are a useful metric mostly in borderline AET, albeit not enough by itself to predict response to therapy.[161,162] Although intermediate values of both metrics taken alone are inconclusive for GERD diagnosis, thresholds have been arbitrary defined and consistently differ between centers and world regions.[163] Patients with normal EGD and GERD symptoms can have true NERD on the basis of abnormal AET in 40% of cases, while the remaining may have functional esophageal disorders.[8] Using MII-pH metrics such as esophageal AET, number of reflux episodes and reflux-symptom association analysis, NERD, reflux hypersensitivity, and functional heartburn represented 32%, 42%, and 26%, respectively, of PPI refractory patients with GERD symptoms.[164]

Statement 21: In patients with proven GERD and persistent symptoms on PPI therapy, esophageal manometry and 24-hour pH-impedance on therapy are requisite to distinguish refractory GERD from functional esophageal disorders.

In patients with proven GERD and persisting symptoms (heartburn, non-cardiac chest pain), MII-pH should be performed on PPI to understand if persisting symptoms are reflux related.[9,161] When testing is performed on PPI therapy, the use of MII-pH is required to detect the presence of weakly acidic reflux, which could contribute to reflux-symptom association[17] and will not be detected by pH monitoring alone. Persistent pathological acid reflux is defined by the Lyon consensus as AET >6%, and inconclusive GERD as AET 4%–6%. These cutoffs were selected because of the paucity of data regarding normal values in healthy controls studied of PPI therapy, and the actual AET threshold defining refractory GERD may be closer to 4% or even lower. Previous data, using an AET threshold of 4.2% reported abnormal AET in 9%–25% of PPI non-responders,[13,116] interpreted as inadequate suppression of gastric acid secretion. However, concordant normative AET data on reflux monitoring performed on PPI therapy are limited, and lower AET thresholds may be indicative of refractory GERD. Persistent elevated AET can result from poor adherence, suboptimal dosing time, or genetic factors as explained elsewhere in this document.

Patients with non-cardiac chest pain treated with PPIs may have functional esophageal disorders if chest pain persists after AET normalizes, and only 0%–17% have PPI response in the absence of documented GERD.[165] Approximately 70% of non-cardiac chest pain patients have a normal esophageal manometry[166,167]; in the remainder, hypercontractile peristalsis, hypotensive LES, and non-specific esophageal motor disorders may be encountered.[168]

Similar to typical GERD symptoms, persisting extraesophageal symptoms in patients with proven GERD on PPI are investigated with MII-pH of PPI with the aim of demonstrating inadequate acid suppression or a temporal relationship between reflux episodes and symptoms (eg, for cough). Unfortunately, the yield of symptom index (SI) and symptom association probability (SAP) is low when extraesophageal symptoms are not discrete in onset as with hoarseness or laryngitis.[169] Of PPI reflux monitoring with elevated numbers of reflux episodes (>80) has been demonstrated to predict symptom improvement from invasive antireflux therapy, while physiologic numbers of reflux episodes (<35–40) are associated with satisfaction with therapy.[12]

If of PPI MII-pH demonstrates normal AET and physiologic numbers of reflux episodes, refractory GERD is excluded and an overlap with functional esophageal disorders should be suspected. Reflux-symptom association analysis can help to distinguish between reflux hypersensitivity and functional heartburn, with the former having a reflux-related pathogenesis. The distinction between NERD and reflux hypersensitivity continues to be studied. Some studies have demonstrated symptom improvement with GERD management within patients fulfilling ROME IV criteria for reflux hypersensitivity.[170,171] Others have demonstrated a higher prevalence of rumination among reflux hypersensitivity presenting with regurgitation.[98] Yet others have demonstrated similar psychological profiles between functional heartburn and reflux hypersensitivity.[172] These data suggest that reflux hypersensitivity might be a heterogeneous category, but more research is needed to clarify which patients with reflux hypersensitivity require GERD management vs. neuromodulators vs. both.

In patients with proven GERD studied on therapy without esophageal erosions on endoscopy, persistent GERD can reasonably be ruled out when AET and number of reflux episodes are normal, and symptom association indices are negative.

Statement 22: Overlap may be demonstrated between proven GERD (as evidenced by prior abnormal AET off PPIs and/or significant esophagitis) and reflux hypersensitivity or functional heartburn, when pH-impedance monitoring is performed on PPI therapy.

About 10%–15% of patients with erosive reflux disease and up to 50% of patients with NERD remain symptomatic despite PPI treatment.[61,142,173] However, persistent pathological reflux is uncommon, and MII-pH analysis of PPI typically demonstrates normal AET and low numbers of reflux events.[8,93] In patients with a normal AET on pH-impedance monitoring on therapy, SI and SAP may provide evidence of a clinically relevant association between reflux episodes and symptoms.

Reflux hypersensitivity is characterized by normal AET, but positive association between symptoms and reflux episodes, in contrast with functional heartburn wherein both SI and SAP are negative. When reflux-symptom association is analyzed, reflux hypersensitivity or functional heartburn may be identified,[174,175] accounting for 12.5%-36% and 62.5%, respectively, in studies of PPI non-responders with documented GERD studied on PPIs.[13,116] These data support the concept that an overlap between GERD, reflux hypersensitivity, and functional heartburn exists, and identification of these conditions is important to understand the reason for PPI failure and to offer alternative treatments.

Statement 23: In patients with inconclusive "of PPI" pH-impedance findings, other impedance parameters including symptom association probability, post-reflux swallow-induced peristaltic wave (PSPW) index, and mean nocturnal baseline impedance (MNBI) may help identify patients with refractory GERD.

Standard MII-pH metrics may not be able to discriminate between physiological and pathological reflux, and gray areas exist, including AET between 4%–6% and number of reflux episodes between 40 and 80/24-h. Reflux-symptom association may increase confidence in a reflux diagnosis when standard metrics are inconclusive. When positive, both SAP and SI have been shown to be predictive of the success of both medical and surgical therapy.[17,176]

Recently, two metrics have been integrated to MII-pH analysis: the post-reflux swallow-induced peristaltic wave (PSPW) index and the mean nocturnal baseline impedance (MNBI). They are two independent indicators of reflux-mediated symptoms that increase the diagnostic yield of impedance testing performed off PPI therapy.[174,175,177–180] PSPW index and MNBI values also correlate with poorly controlled GERD on PPIs, with a gradient of values that segregate patients with functional heartburn from NERD, healed reflux esophagitis, and refractory esophagitis.[174] The PSPW index also separates erosive esophagitis from NERD patients and both groups from functional heartburn.[175] In PPI non-responders on ongoing therapy, the PSPW index is significantly lower in refractory esophagitis compared to healed reflux esophagitis and NERD and is the only MII-pH parameter associated with PPI refractory mucosal damage.[181]

Statement 24: Esophageal motility should be assessed using high-resolution manometry in patients with refractory GERD symptoms. High-resolution manometry can rule out major esophageal motility disorders and demonstrate esophagogastric junction and esophageal body motor abnormalities associated with GERD.

HRM does not represent a diagnostic test for GERD, since most patients with reflux disease have normal manometry or minor motility disorders.[9] However, HRM is routinely performed prior to ambulatory reflux monitoring [182] to identify anatomical location and morphology of the EGJ.[183] In this setting, HRM has the important role of ruling out achalasia and other major esophageal motility disorders that can mimic GERD.[184]

Several EGJ and esophageal body abnormalities have been associated with GERD. Separation between LES and crural diaphragm can result in a significant increase in esophageal reflux burden and higher likelihood of positive reflux-symptom association, especially when separation is >3 cm.[185] The EGJ can also be hypotensive, with or without a hiatal hernia. The EGJ contractile integral (EGJ-CI) is a novel HRM metric that defines the efficacy of EGJ as an antireflux barrier. EGJ-CI values correlate with the presence of esophagitis and abnormal ambulatory reflux monitoring scores[186] and distinguish functional heartburn from refractory GERD.[187]

Esophageal body hypomotility disorders are the most frequent abnormal findings in GERD.[182] The severity of reflux symptoms and AET values increases proportionally with defects of esophageal peristalsis like weak, failed, and absent peristalsis.[188,189] The likelihood of abnormal peristalsis is higher in erosive esophagitis and BE compared to NERD, demonstrating the role of esophageal body in reflux clearance.[182,190] Finally, contraction reserve, assessed using multiple rapid swallows (MRS) and contraction vigor augmentation ratio (MRS distal contractile integral: single swallow distal contractile integral >1), may add relevant information. Erosive esophagitis is frequently associated with ineffective contraction reserve compared to NERD and healthy controls.[191] Absence of contraction reserve also correlates with higher AET in NERD and seems to predict the development of ineffective motility after antireflux surgery.[192–194]

Statement 25: When rumination is suspected in patients with persistent regurgitation on PPI therapy, manometry with impedance, ambulatory, or stationary (postprandial), is indicated to distinguish rumination from GERD.

Impedance with HRM (high-resolution impedance manometry, HRIM) allows complete evaluation of esophageal function, bolus transit, and clearance. When performed during postprandial periods or following test meals, HRIM can be helpful to identify conditions that can mimic GERD, such as rumination syndrome and supragastric belching.[195] This step is important, considering that these disorders can benefit more from behavioral interventions than from medical therapy or surgery. In a retrospective study using a non-standardized test meal, rumination events were reported in 20% of cases of GERD patients, who were diagnosed as PPI non-responders.[14] A distinct rumination pattern has been described on MII-pH monitoring, with early postprandial reflux episodes with high proximal extent, weakly acidic reflux transitioning to acid reflux postprandially, and reflux-symptom association with symptoms earlier by rumination patients compared to GERD patients.[103]

Statement 26: In asymptomatic patients with untreated Barrett's esophagus, testing for persisting reflux on PPIs is not recommended.

Patients with BE are more likely to have ongoing pathological acid reflux on reflux monitoring performed on PPIs despite being less symptomatic, compared with GERD patients without BE.[196] Indeed, 20%–25% of patients with BE have persistent abnormal reflux on MII-pH despite double-dose PPI therapy.[197,198] In BE, long-term PPI therapy is advisable to reduce progression to esophageal adenocarcinoma.[199] Thus, MII-pH will not modify management of asymptomatic BE patients, although MII-pH findings on therapy may prompt escalation of antireflux management in BE patients with ongoing reflux symptoms. In contrast, MII-pH may be relevant

following radiofrequency ablation of Barrett's mucosa since persistent or recurrent intestinal metaplasia/dysplasia is associated with poorly controlled GERD.[198,200]

8 | MANAGEMENT

8.1 | Lifestyle interventions in GERD

Statement 27: Weight loss reduces esophageal acid exposure and reflux symptoms, even in non-obese GERD patients.

Small randomized controlled trials (RCTs) comparing weight loss using gastric balloons vs. sham treatment combined with lifestyle measures in severely obese individuals reported reduced esophageal acid exposure with weight loss (Table 4).[201,202] A larger RCT comparing structured weight loss program vs. telephone-based group conference on weight management in obese participants showed a significant improvement in prevalence of reflux symptoms (37% to 15%, $p < 0.01$), and Reflux Disease Questionnaire Symptom Score ($p < 0.01$) after 6 months of weight loss in both groups.[203] An uncontrolled prospective cohort study of 8 extremely obese patients demonstrated AET reduction (5.1% to 2.5%, $p = 0.022$) and improved reflux symptoms (Distress Subscale of Gastroesophageal Reflux Disease Symptom Assessment Scale from 1.28 to 0.72, $p = 0.0004$) after 4 days on a very low-carbohydrate diet and a mean weight loss of 1.7 kg.[204] In another study of 34 patients with normal body weight and reflux symptoms, a correlation was found between reflux-symptom reduction and weight loss following dietary advice (modified DeMeester questionnaire, $r = 0.548$, $p < 0.001$).[205]

Two large prospective population-based cohort studies showed that weight reduction decreased reflux symptoms depending on the degree of weight loss. An observational cohort study of 10,545 women showed reduced risk of reflux symptoms among women who had a decrease in BMI compared to women with no BMI change (odds ratio (OR) 0.64, 95% confidence interval (CI) 0.42–0.97 with >3.5 units decrease in BMI, P for trend <0.001).[206] Another prospective population-based cohort study of 29,610 participants also showed a dose-dependent association between degree of weight loss and improvement of reflux symptoms (OR 2.42, 95% CI 1.88–3.11 with >3.5 units decrease in BMI, P for trend <0.001).[207]

There are studies with the opposite findings, including a small RCT suggesting that a mean 10.8 kg weight loss in borderline obese patients (mean BMI = 31.4) with GERD did not have a significant impact on symptoms, esophagitis, or pH measurements following randomization to either a 430 kcal/day diet for 6 months ($n = 10$) or not ($n = 9$).[208] Additionally, a prospective population-based cohort study of 637 individuals showed no association between weight loss and reflux symptoms, although weight loss was self-reported and may not be accurate.[209] Thus, in sum, weight loss reduces both esophageal acid exposure and reflux symptoms independent of the initial body weight, but it is not known if these benefits are also seen in patients with refractory GERD.

TABLE 4 Management of refractory GERD

Lifestyle interventions in GERD
Statement 27: Weight loss reduces esophageal acid exposure and reflux symptoms, even in non-obese GERD patients
Statement 28: There is insufficient evidence to assess the value of smoking cessation or discontinuation of alcohol consumption in treating refractory GERD symptoms
Statement 29: Symptomatic GERD patients should be recommended postural measures, including avoiding eating dinner close to bedtime, elevation of the head end of the bed by at least 20 cm, and sleeping in the left lateral position using sleep positional therapy.
Optimizing acid-suppressive therapy
Statement 30: PPIs are more effective in reducing GERD symptoms when taken before meals, before breakfast with once-daily dosing, and before breakfast and 30–60 min before dinner with twice-daily dosing.
Statement 31: The effectiveness of PPIs in GERD is related to their ability to raise the intragastric pH to >4 for a substantial fraction of the day. Any standard-dose PPI taken twice-daily (before breakfast and before dinner) controls intragastric pH more effectively than the same standard-dose PPI taken once daily.
Statement 32: The subset of refractory GERD patients with persistent esophagitis on EGD or persistent esophageal acid exposure on pH monitoring should be treated with a more potent PPI regimen.
Statement 33: Potassium-competitive acid blockers (P-CABs) taken once-daily control intragastric pH more effectively and rapidly than any standard-dose PPI taken once daily and have potential value in refractory GERD.
Adjunctive medical therapy
Statement 34: Short-term nighttime H_2RA can be considered for refractory nocturnal reflux symptoms, but the evidence is indirect and very limited
Statement 35: Prokinetics have no added value in the treatment of patients with PPI refractory reflux symptoms.
Statement 36: Baclofen has proven efficacy in PPI refractory GERD, but side effects often limit its use.
Statement 37: There is some evidence that the topical mucosal preparations containing alginate, and protective agents reduce symptoms in patients with PPI refractory GERD.
Surgical and Interventional Management of GERD
Statement 38: Antireflux surgery, including laparoscopic fundoplication and magnetic sphincter augmentation, improves refractory GERD symptoms, particularly regurgitation, in patients with proven GERD.
Statement 39: Transoral incisionless fundoplication (TIF) demonstrates short-term and limited longer-term evidence for benefit in improving regurgitation in carefully selected patients, but acid exposure times are not normalized.
Statement 40: Overall benefits from radiofrequency application (Stretta) in refractory GERD are mixed, with variable symptom improvement, but limited objective improvement in acid burden or manometric EGJ features.

Statement 28: There is insufficient evidence to assess the value of smoking cessation or discontinuation of alcohol consumption in treating refractory GERD symptoms.

Being a current or former smoker is considered a risk factor for reflux symptoms,[210,211] and smoking cessation is associated with decreased reflux symptoms in normal weight individuals on medical treatment, compared to those who continued daily smoking (OR 5.67, 95% CI 1.36–23.64).[212] A similar association has not been described in overweight or obese individuals, suggesting that body weight is a more important factor than smoking status. However, smoking is known to have clear effects on GERD pathogenesis, and advocating for smoking cessation has broader health benefits beyond just GERD management.

Among studies looking at alcohol use as a risk factor for reflux symptoms, one suggested that alcohol caused fewer reflux symptoms if consumed with food,[211] while another demonstrated that drinking spirits (but not wine) a few times a week exacerbates reflux.[213] However, in a large epidemiological cohort study, alcohol, defined as spirits, beer, or wine, was not a risk factor for reflux symptoms.[214]

Other dietary elements including coffee,[214] carbonated beverages,[215] or table salt intake[216] have not been linked to reflux symptoms and do not need universal exclusion when not consistently triggering symptoms.

Statement 29: Symptomatic GERD patients should be recommended postural measures, including avoiding eating dinner close to bedtime, elevation of the head end of the bed by at least 20 cm, and sleeping in the left lateral position using sleep positional therapy.

Avoiding late evening meals is recommended in several reflux guidelines.[5,59] A crossover study of 30 patients randomized to a late meal (2 h before bedtime) vs. an early meal (6 hours before bedtime) showed significantly higher supine reflux on pH monitoring after the late evening meal (mean change 5.2%, $p = 0.002$),[217] supporting earlier dinner times in symptomatic GERD patients.

A crossover RCT of 15 GERD participants showed that elevation of the head of the bed by a 10-inch wedge decreased esophageal AET compared to a flat position (15% and 21%, respectively, $p < 0.05$).[218] Another study measuring the effect of 20-cm elevation of the head end of the bed demonstrated a significant but small effect on nocturnal acid exposure (15.0 ± 8.4 vs. 13.7 ± 7.2; $p = 0.001$) and symptom score.[219] Both studies support elevating the head end of the bed while supine.

Several studies have shown that reflux is more likely to occur in the right lateral position compared to the left lateral position.[220,221] A dedicated pillow that forces the user to sleep on the left lateral position and simultaneously increases the head end of the subject's bed has shown a reduction in nocturnal reflux episodes in healthy volunteers.[222] In patients with PPI refractory nocturnal reflux symptoms, 2-week use of the sleep pillow resulted in a substantial reduction in nocturnal and overall reflux symptoms on validated questionnaires, and 91% continued to use the pillow at 3-month follow-up.[223] Therefore, sleep positional therapy seems to be effective in patients with GERD and nocturnal symptoms.

While these recommendations are part of general lifestyle adjustments in GERD patients, their impact on refractory GERD as defined in this consensus document remains unknown.

9 | OPTIMIZING ACID-SUPPRESSIVE THERAPY

Statement 30: PPIs are more effective in reducing GERD symptoms when taken before meals, before breakfast with once-daily dosing, and before breakfast and 30–60 minutes before dinner with twice-daily dosing.

All PPIs are acid labile molecules with an enteric coating to prevent rapid degradation in the stomach, with rapid absorption from the small bowel distal to the stomach. Consequently, the need for gastric emptying introduces a delay in onset of action, which will be further prolonged if taken with food or after a meal. Once absorbed, the magnitude of acid suppression correlates with the area under the curve (AUC) of serum PPI concentration vs time. Meals reduce AUC for esomeprazole, estimated at 43%–53% and lansoprazole, estimated at 50%–70%. While AUC is unchanged for pantoprazole and rabeprazole taken with a meal, the T_{max} is still delayed from retention in the stomach. All PPIs have a relatively short serum half-life, on the order of 1 h, and their prolonged duration of action is related to covalent binding and inactivation of the target proton pump rather than drug accumulation with repeated doses.[224] Acid production is only restored through endogenous resynthesis of the proton pumps with a half-life of production of about 2 days.[225] The exception is rabeprazole, which has a shorter duration of action since it dissociates from the proton pump to a greater extent and hence allows "recovery".

Together, these pharmacokinetic and pharmacodynamic considerations provide indirect evidence highlighting the importance of adherence to an optimal before meal PPI dosing strategy in refractory GERD. Furthermore, adherence to before meal dosing is equally important with every PPI dose because there is no drug accumulation with repeated dosing.

Statement 31: The effectiveness of PPIs in GERD is related to their ability to raise the intragastric pH to >4 for a substantial fraction of the day. Any standard-dose PPI taken twice-daily (before breakfast and before dinner) controls intragastric pH more effectively than the same standard-dose PPI taken once daily.

Studies relating PPI effectiveness in GERD to their ability to control intragastric pH conclude that their relative effectiveness depends on how consistently they maintain intragastric pH >4 throughout the day, varying from 35% to 60% of the day (at steady state) among available standard-dose PPIs.[7,62,226] Based on this physiomarker, PPIs are substantially more effective than H_2RAs in treating peptic ulcer disease, in healing esophagitis, and in suppressing gastric acid secretion. This physiomarker is reliable in assessing PPI effectiveness, particularly in healing and maintenance therapy of high-grade esophagitis, and has been used widely to compare PPI efficacy in marketing studies.[227] However, except in rare circumstances, intragastric pH is a useful a surrogate endpoint for clinical trials rather than clinical practice.

The physiomarker of maintaining gastric pH > 4 is the basis for comparing twice-daily to once-daily PPI regimens, since there are no large clinical GERD trials comparing dosing frequency using clinical

endpoints. In a recent meta-analysis of 25 studies with 592 subjects receiving twice-daily PPI therapy, the weakest standard-dose PPI (pantoprazole 40 mg) taken twice-daily maintained intragastric pH >4 for a weighted average of 68% of the day (3 studies), slightly more efficacious than the strongest standard-dose PPI (esomeprazole 40 mg) taken once daily, which maintained the gastric pH >4 for 66% of the day (18 studies).[7] Twice-daily esomeprazole 40 mg maintained gastric pH >4 for a weighted average of 88% of the day in 5 studies and intermediate strength PPIs taken twice-daily fell between the pantoprazole and esomeprazole values.

Statement 32: The subset of refractory GERD patients with persistent esophagitis on endoscopy or persistent esophageal acid exposure on pH monitoring should be treated with a more potent PPI regimen.

Inadequate acid suppression despite a 4- to 8-week course of standard-dose PPI partially accounts for the refractory GERD population, clinically identified by having either persistent esophagitis on 8-week follow-up endoscopy or having >6% esophageal acid exposure on a pH metry study performed on standard-dose PPI.[9] Further, esophagitis healing rates in PPI trials diminish as the severity of esophagitis increases from A to D in the Los Angeles classification. The first step in managing these patients consists of confirming adherence to optimal PPI use. Refractory GERD patients improve with therapy that increases the fraction of the day with gastric pH maintained >4, be that a more potent PPI, higher dose PPI, twice-daily PPI, or a potassium-competitive acid blocker (P-CAB).[7] Most studies have inferred superiority of one PPI regimen over another by using the physiomarker of the fraction of the day that the gastric pH is maintained >4. Although trends are usually evident, clinical trials of healing reflux esophagitis have not been powered to show relatively small differences in healing rates of the enrolled patients with LA C/D disease. What little data do exist, however, supports the relevance of the gastric pH >4 time physiomarker. An example of this is a Japanese study of patients unhealed with standard-dose PPI, which demonstrated healing after switching to 8 weeks of rabeprazole 10 mg or 20 mg bid and significantly better maintenance of healing among the healed patients in the subgroup randomized to 10 mg bid vs 10 mg qd of rabeprazole (74% vs 45%, $p < 0.001$).[228]

Statement 33: Potassium-competitive acid blockers (P-CABs) taken once-daily control intragastric pH more effectively and rapidly than any standard-dose PPI taken once daily and have potential value in refractory GERD.

P-CABs have been developed to overcome limitations of PPI pharmacotherapeutics. P-CABs block the K+ exchange channel of the proton pump, resulting in a very rapid, competitive, and reversible inhibition of acid secretion. Although several P-CABs (revaprazan, tegoprazan, fexuprazan) are in various stages of clinical development, vonoprazan is the furthest along and is currently approved for use in Japan for treatment of gastric or duodenal ulcers, for healing esophagitis, for maintenance of esophagitis healing, for prevention of aspirin or NSAID induced injury, and for *H. pylori* eradication.[229] Vonoprazan is acid stable and rapidly absorbed regardless of timing with respect to meals, reaching C_{max} in 1.5–2.0 h. It dissociates slowly from proton pumps with a half-life of almost 8 h.[230] Further, its high pKa (>9) promotes accumulation in parietal cell secretory canaliculi, where it competitively inhibits both active and resting proton pumps.[231] It is metabolized primarily by CYP2C19. Based on the physiomarker of maintaining gastric pH>4, vonoprazan is more potent and longer acting than any standard-dose PPI. Vonoprazan 20 mg maintained intragastric pH >4 for about 63% of the day on day 1, increasing to 84% after 7 days. In Western populations, after 7 days of therapy with 10, 20, 30, and 40 mg of vonoprazan daily, gastric pH was >4 for 60.2%, 85.2%, 90.1%, and 93.2%, respectively.[6,229]

In a RCT of vonoprazan vs lansoprazole 30 mg daily, higher doses (20 mg, 40 mg daily) of vonoprazan were numerically superior (100% for 20 mg, 96% for 40 mg) to lansoprazole (93.5%) in healing LA C/D esophagitis after 8 weeks; the differences were greater, but still not statistically significant at the 2-week time point (82.6% lansoprazole vs 96% for both doses of vonoprazan).[232] Vonoprazan improves refractory GERD symptoms mainly by reducing acidic reflux episodes, but is not consistently effective, especially when reflux episodes with pH 4–5 persist.[233] The approved doses in Japan are 10 mg and 20 mg.

10 | ADJUNCTIVE MEDICAL THERAPY

Statement 34: Short-term nighttime H_2RA can be considered for refractory nocturnal reflux symptoms, but the evidence is indirect and very limited.

The comparative potency of H_2RA regimens for healing peptic ulcers depends on how effectively they maintain intragastric pH >4 throughout the day, making that a reliable physiomarker of their effectiveness in peptic ulcer disease. However, that degree of acid inhibition has proven inadequate to heal esophagitis, particularly high-grade esophagitis. Adjunctive bedtime H_2RA therapy added to a PPI regimen increases duration and degree of suppression of intragastric pH, an indirect measure of efficacy for GERD treatments. In a retrospective cohort study, addition of nighttime ranitidine 300 mg or famotidine 40 mg improved overall symptoms (72%) and nighttime symptoms (74%), though 13% discontinued H_2RA after 1 month due to tachyphylaxis.[234] When compared to PPI alone, addition of nighttime H_2RA for PPI refractory symptoms significantly reduced nocturnal acid breakthrough (17% vs. 64%) and percent intragastric time pH <4 (18% vs. 31.5%).[235] Total esophageal acid exposure was not significantly reduced (1.9% vs. 3.3%). Therefore, the evidence is weak and the use of additional H_2RA cannot be recommended in all patients with refractory GERD.[236]

Statement 35: Prokinetics have no added value in the treatment of patients with PPI refractory reflux symptoms.

Several RCTs performed in Asia found no improvement in reflux symptoms with use of adjunctive mosapride (a selective 5-HT_4 receptor agonist) in patients with PPI refractory GERD. Hence, mosapride combination therapy with PPI is no more effective than PPI alone.[237] Reverexepride, also a selective 5-HT_4 receptor agonist,

was no more effective than placebo for symptom control in PPI refractory GERD in two RCTs.[238,239] Another selective 5-HT_4 receptor agonist, prucalopride (4 mg), reduced esophageal acid exposure (3.4 [2.5–5.6] vs 1.7 [0.8–3.5] %, $p < 0.05$) and accelerated gastric emptying (T1/2; 32.7 [27.9–44.6] vs 49.8 [37.7–55.0] min, $p < 0.05$) in a randomized crossover study in 21 healthy male subjects.[240] In a study of four female PPI refractory GERD patients with chronic constipation, 2 mg prucalopride daily reduced total and non-acid reflux episodes with concordant symptom improvement.[241] However, in the absence of a RCT in PPI refractory GERD patients, we conclude that there are insufficient data to make conclusions regarding the efficacy of prucalopride in refractory GERD. In a double-blinded RCT, the D_2-receptor antagonist domperidone (10 mg three times daily) plus omeprazole (twice daily) provided superior symptom relief compared to omeprazole alone; however, objective measure of GERD symptoms was identical between groups.[242]

Therefore, based on available evidence, prokinetics have no added value in the management of refractory GERD.

Statement 36: Baclofen has proven efficacy in PPI refractory GERD, but side effects often limit its use.

The GABA-B agonist baclofen is the best-studied TLESR inhibitor, which has been shown to reduce reflux symptoms, esophageal acid exposure, and TLESRs in patients with PPI refractory GERD.[243] In addition to reducing numbers of reflux episodes and heartburn, baclofen may have particular benefit in regurgitation-predominant refractory symptoms and in belching.[244] However, side effects (especially drowsiness and somnolence) and need for 3 doses a day for optimal effect make baclofen less suitable for treatment of a benign disorder such as GERD. Arbaclofen[245] and lesogaberan[246] were designed to overcome the unfavorable pharmacokinetics and side effect profile of baclofen but development was halted due to side effects and disappointing results.

Statement 37: There is some evidence that topical mucosal preparations containing alginate, and protective agents reduce symptoms in patients with PPI refractory GERD.

In a RCT, Esoxx (a hyaluronic acid-chondroitin sulfate-based bioadhesive formulation) added to standard-dose PPIs for 2 weeks reduced GERD symptoms in a significant larger proportion of patients compared to placebo (52.6% vs 32.1%, $p < 0.05$) among 154 patients with GERD partially responding to PPI.[247] A RCT in patients with PPI refractory GERD showed that adding the alginate Gaviscon 10 ml 4 times a day resulted in a larger symptom reduction, and lesser number of nights with symptoms compared to placebo.[248] Another RCT demonstrated greater symptom reduction with the alginate-antacid combination Gaviscon double action 10 ml 4 times daily versus placebo, but this could not be confirmed in a larger confirmatory study.[249] The alginic acid delivery system Mirgeal containing glycyrrhetinic acid and anthocyanosides (both of which have mucosal protective properties), in combination with PPI provided greater symptom control for PPI refractory GERD as compared to alginic acid plus PPIs.[250] Altogether, these results suggest that alginates and protective agents prescribed as add-on therapy may be useful in patients with refractory GERD symptoms despite PPI therapy.

11 | SURGICAL AND INTERVENTIONAL MANAGEMENT OF GERD

Statement 38: Antireflux surgery, including laparoscopic fundoplication and magnetic sphincter augmentation, improves refractory GERD symptoms, particularly regurgitation, in patients with proven GERD.

Laparoscopic fundoplication is comparable to long-term PPI therapy in well-characterized GERD[251,252] with as many as 60% undergoing fundoplication remaining off antisecretory therapy for >15 years of follow-up in one study,[253] although others report that up to 62% resume antisecretory therapy over follow-up.[254] In a prospective study of 366 patients with refractory heartburn who were enrolled in a Veterans Administration study, 99 (27%) had functional heartburn on the basis of negative esophageal testing including MII-pH on acid suppression, while 23 (6%) had non-GERD esophageal disorders, and 7 (2%) had esophageal motility disorders.[3] Of the remainder 78 patients with refractory symptoms randomized to therapy, 67% improved with laparoscopic fundoplication, compared to 28% with active medical management (omeprazole, with baclofen and/or desipramine), and 12% with control medical management (omeprazole with placebo) ($p \leq 0.007$).[3] Laparoscopic fundoplication improved numbers of reflux episodes on pH-impedance monitoring (76/day to 1.6/day, $p < 0.001$) and GERD symptoms using GERD health-related quality of life (18.6 to 1.6, $p = 0.015$) in 31 well-characterized GERD patients refractory to medical management.[255] Thus, proper preoperative evaluation and appropriate patient selection are critical to treatment success with fundoplication, and ambulatory reflux monitoring is important as part of this evaluation. Fundoplication improves both acidic and weakly acidic reflux episodes, in contrast to PPI therapy, which only increases the pH of reflux episodes, and does not stop the reflux episodes themselves.[256] Recommendations regarding specific types of fundoplication are outside the scope of this report.

Magnetic sphincter augmentation (MSA) has recently emerged an alternate minimally invasive surgical option, which normalized distal esophageal acid exposure in 58% at one year, and reduces PPI usage by at least half in 93%.[257] At 5 years, heartburn decreased from 89% at baseline to 12%; regurgitation decreased from 57% to 1%. Daily PPI use decreased from 100% at baseline to 15.3% at 5 years, and double-dose PPI use decreased from 36% to 2.4%.[258] Dysphagia is a potential consequence, with prevalence of 4% 3 years after MSA, although prevalence is as high as 68% in the early postoperative period.[257,259] Surgery for MSA removal was required in 3.4%–7% because of dysphagia, continued reflux, or chest pain.[258,259]

Recent MSA studies have targeted regurgitation-predominant GERD poorly responsive to PPI therapy. In a prospective study of 152 patients with PPI refractory regurgitation, 50 patients randomized to MSA reported 89% improvement in regurgitation at 6 months on validated questionnaires compared to 10% improvement in 102 patients randomized to twice-daily PPI.[260] At 6 months, PPI-treated patients were allowed to cross over to the MSA arm; at the 12-month time point, 96% on MSA

reported improvement, compared to 19% on PPI. Acid exposure time decreased from 10.7% to 1.3% at 1 year, while 7% reported dysphagia; no patient had the MSA device removed. Thus, MSA has potential to improve refractory GERD-related regurgitation. Despite these potential benefits, it is important to highlight that MSA is expensive and requires surgery. While early studies excluded large hiatus hernias, hernia repair can be performed in conjunction with MSA implantation. MSA also has potential for device erosion and migration in addition to dysphagia.

Obese patients with refractory GERD can benefit from Roux-en-Y gastric bypass surgery, which effectively disconnects the esophagus from the body of the stomach and reliably reduces esophageal reflux burden, while also insuring weight loss.[261,262] Roux-en-Y bypass surgery is safer than laparoscopic fundoplication in morbidly obese patients, with less postoperative complications, despite similar hospital costs, length of stay, and mortality.[263] Gastric-sleeve surgery, in contrast, can worsen GERD symptoms.

Statement 39: Transoral incisionless fundoplication (TIF) demonstrates short-term and limited longer-term evidence for benefit in improving regurgitation in carefully selected patients.

In a randomized study, 67% undergoing TIF had improvement in regurgitation symptoms compared to 45% improvement with sham surgery and PPI therapy, with better control of esophageal pH, but with similar post-procedure GERD scores.[264] The TEMPO trial evaluated the efficacy of TIF compared to high dose PPIs, using a randomized, crossover design in 63 patients with persisting GERD symptoms despite PPI for 6 months, and abnormal 48-hour pH monitoring, enrolled from 7 US institutions.[265] There were significant reductions in regurgitation scores, GERD-HRQL score, and reflux-symptom index in those that underwent TIF compared to PPI therapy alone at 6 months. In a third study, atypical GERD symptoms improved in 80% of patients at 5 years, while 34% remained on daily PPI therapy.[266] This study excluded obese patients with BMI over 35 kg/m^2, advanced grade esophagitis (LA grade C or D), large hiatus hernias (>2 cm, or Hill grade III or IV), and long segment BE (>2 cm), suggesting that these characteristics may not be optimal for TIF. In a 10-year follow-up study, patients who underwent TIF had lower GERD-HRQL scores compared to scores obtained pre-TIF off PPI therapy. In those that had stopped PPI, complete response rate fell by 20% but this was not statistically significant.[267] A systematic analysis of 18 observational and randomized trials utilizing both TIF 1.0 and 2.0 demonstrated benefit of TIF (66%) over PPI and sham procedures (30%), with reduction in reflux episodes, although acid exposure was not improved compared to PPI therapy.[268]

Statement 40: Overall benefits from radiofrequency application (Stretta) in refractory GERD are mixed, with variable symptom improvement, but limited objective improvement in acid burden or manometric EGJ features.

Early studies of radiofrequency energy delivery (RFED) to the distal esophagus demonstrated improvement in health-related quality of life (HRQOL) scores in 61% of patients who underwent RFED compared to 30% undergoing a sham procedure, but esophageal acid exposure and acid-suppressive medication use were not impacted at 6-month follow-up.[269] A recent randomized sham-controlled study showed no benefit of RFED in patients with refractory heartburn, most of them having functional esophageal disorders.[270] In a meta-analysis of 28 studies that included both randomized controlled studies and open-label cohort studies, RFED significantly reduced HRQOL scores, while also reducing PPI usage and incidence of erosive esophagitis on endoscopy.[271] In another meta-analysis limited to randomized studies comparing RFED to PPI therapy or sham procedures, the quality of evidence was found to be poor, with no improvement in AET, LES pressures, ability to stop medications or HRQOL.[272]

RFED appears to be generally safe, with only limited reports of chest discomfort, fever, esophageal ulceration, and gastroparesis. RFED is available commercially and could potentially be considered for patients without large hiatus hernia or GERD complications (stricture, BE), who either are not candidates for surgery, or prefer a minimally invasive endoscopic approach. However, Gastrointestinal and Surgical Societies recommend extensive patient discussions regarding costs and the mixed nature of available outcome data before performing RFED,[273] reflecting the mixed nature of available supportive data. The optimal clinical context wherein RFED is indicated or beneficial remains unclear.

12 | CONCLUSIONS

While persisting symptoms are frequently encountered during PPI therapy of esophageal symptoms, not all refractory symptoms represent refractory GERD. Understanding the epidemiology of refractory GERD as opposed to refractory GERD symptoms and the pharmacotherapeutics of antisecretory therapy will help the clinician select the optimal approach to refractory symptoms (Figure 2) and determine the most efficient testing modalities that will help plan an effective management approach (Figure 1). Along the way, conditions that mimic GERD are diagnosed and appropriately managed, and refractory GERD is appropriately addressed with optimized medical or procedural therapy.

CONFLICT OF INTERESTS

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Phathom Pharmaceuticals; Daewood; Patent on mucosal integrity by Vanderbilt. RY: Consultant: Medtronic, Ironwood Pharmaceuticals, Diversatek; Research support: Ironwood Pharmaceuticals; Advisory Board: Phathom Pharmaceuticals. CPG: Consulting: Medtronic, Diversatek, Ironwood, ISOThrive, Quintiles.

AUTHOR CONTRIBUTIONS

All authors proposed statements, drafted literature review, and approved the final version of the manuscript.

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