CME

ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) continues to be among the most common diseases seen by gastroenterologists, surgeons, and primary care physicians. Our understanding of the varied presentations of GERD, enhancements in diagnostic testing, and approach to patient management have evolved. During this time, scrutiny of proton pump inhibitors (PPIs) has increased considerably. Although PPIs remain the medical treatment of choice for GERD, multiple publications have raised questions about adverse events, raising doubts about the safety of long-term use and increasing concern about overprescribing of PPIs. New data regarding the potential for surgical and endoscopic interventions have emerged. In this new document, we provide updated, evidence-based recommendations and practical guidance for the evaluation and management of GERD, including pharmacologic, lifestyle, surgical, and endoscopic management. The Grading of Recommendations, Assessment, Development, and Evaluation system was used to evaluate the evidence and the strength of recommendations. Key concepts and suggestions that as of this writing do not have sufficient evidence to grade are also provided.

INTRODUCTION

A lot has changed, much remains the same. Gastroesophageal reflux disease (GERD) continues to be among the most common diseases seen by gastroenterologists, surgeons, and primary care physicians. Since publication of the last American College of Gastroenterology guideline on reflux management (1), clinically important advances in surgical and endoscopic therapy of GERD have emerged. Our understanding of the varied presentations of GERD, enhancements in diagnostic testing, and approach to patient management have evolved. During this time, scrutiny of proton pump inhibitors (PPIs) has increased considerably. Although PPIs remain the medical treatment of choice for GERD, multiple publications have raised questions about adverse events, raising doubts about the safety of long-term use and increasing concern about overprescribing of PPIs. In this new document, we provide updated, evidence-based recommendations and practical guidance for the evaluation and management of GERD, including pharmacologic, lifestyle, surgical, and endoscopic management. The management of functional heartburn and other functional upper gastrointestinal (GI) symptoms is beyond the scope of this guideline. Additional detail regarding esophageal physiologic testing is covered in other guidelines.

Summary and strength of the recommendations can be found in Table 1 with key concepts summarized in Table 2.

METHODS

The guideline is structured in the format of statements that are considered to be clinically important by the content authors for evaluation and treatment of GERD. The authors developed PICO questions and performed a literature search for each question with assistance from a research librarian. The Grading of Recommendations, Assessment, Development, and Evaluation process was used to assess the quality of evidence for each statement (3). The quality of evidence is expressed as high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence, and precision of the estimate of effect (4). A strength of recommendation is given as either strong (recommendations) or conditional (suggestions) based on the quality of evidence, risks vs benefits, feasibility, and costs taking into account perceived patient and population-based factors (5).

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Furthermore, a narrative evidence summary for each section provides important details for the data supporting the statements.

Our goal is to showcase a document that offers best practice recommendations for clinicians caring for patients with GERD.

These guidelines are established to support clinical practice and suggest preferable approaches to a typical patient with a particular medical problem based on the currently available published literature. When exercising clinical judgment, particularly when treatments pose significant risks, health care providers should incorporate this guideline in addition to patient-specific medical comorbidities, health status, and preferences to arrive at a patient-centered care approach.

DIAGNOSIS OF GERD

The below recommendations for the diagnosis of GERD are also illustrated in Figure 1.

Recommendations

1. For patients with classic GERD symptoms of heartburn and regurgitation who have no alarm symptoms, we recommend an 8-week trial of empiric PPIs once daily before a meal (strong recommendation, moderate level of evidence).
2. We recommend attempting to discontinue the PPIs in patients whose classic GERD symptoms respond to an 8-week empiric trial of PPIs (conditional recommendation, low level of evidence).
3. We recommend diagnostic endoscopy, ideally after PPIs are stopped for 2–4 weeks, in patients whose classic GERD symptoms do not respond adequately to an 8-week empiric trial of PPIs or whose symptoms return when PPIs are discontinued (strong recommendation, low level of evidence).
4. In patients who have chest pain without heartburn and who have had adequate evaluation to exclude heart disease, objective testing for GERD (endoscopy and/or reflux monitoring) is recommended (conditional recommendation, low level of evidence).
5. We do not recommend the use of a barium swallow solely as a diagnostic test for GERD (conditional recommendation, low level of evidence).
6. We recommend endoscopy as the first test for evaluation of patients presenting with dysphagia or other alarm symptoms (weight loss and GI bleeding) and for patients with multiple risk factors for Barrett's esophagus (strong recommendation, low level of evidence).
7. In patients for whom the diagnosis of GERD is suspected but not clear, and endoscopy shows no objective evidence of GERD, we recommend reflux monitoring be performed off therapy to establish the diagnosis (strong recommendation, low level of evidence).
8. We recommend against performing reflux monitoring off therapy solely as a diagnostic test for GERD in patients known to have endoscopic evidence of Los Angeles (LA) grade C or D reflux esophagitis or in patients with long-segment Barrett's esophagus (strong recommendation, low level of evidence).

Key concept

1. We do not recommend high-resolution manometry (HRM) solely as a diagnostic test for GERD.

Defining GERD

A single unifying definition of GERD is difficult. In preparing this guideline, we have blended the multiple definitions in the literature to create the following: GERD is the condition in which the reflux of gastric contents into the esophagus results in symptoms and/or complications. GERD is objectively defined by the presence of characteristic mucosal injury seen at endoscopy and/or abnormal esophageal acid exposure demonstrated on a reflux monitoring study.

Pathophysiology of GERD

The pathophysiology of GERD includes a poorly functioning esophagogastric junction; the antireflux barrier composed of the LES and crural diaphragm, coupled with impaired esophageal clearance and alterations in esophageal mucosal integrity. Reflux esophagitis develops when refluxed gastric juice triggers the release of cytokines and chemokines that attract inflammatory cells and that also might contribute to symptoms. Other contributors to GERD symptoms may include decreased salivary production, delayed gastric emptying, and esophageal hypersensitivity. As such, GERD can no longer be approached as a single disease, but one with multiple phenotypic presentations and different diagnostic considerations.

Symptoms

Typical symptoms of GERD include heartburn and regurgitation. Heartburn is the most common GERD symptom and is described as substernal burning sensation rising from the epigastrium up toward the neck. Regurgitation is the effortless return of gastric contents upward toward the mouth, often accompanied by an acid or bitter taste. Although both heartburn and regurgitation are major symptoms of GERD, the genesis of these symptoms is not the same, and the diagnostic and management approaches vary depending on which symptom predominates. Chest pain, indistinguishable from cardiac pain, may present in conjunction with heartburn and regurgitation or as the only GERD symptom. The symptoms of GERD are nonspecific and may overlap or be confused with those of other disorders such as rumination, achalasia, eosinophilic esophagitis (EoE), reflux hypersensitivity, functional disease, cardiac or pulmonary disease, and paraesophageal hernia.

Extraesophageal manifestations of GERD can include laryngeal and pulmonary symptoms such as hoarseness, throat clearing, and chronic cough and conditions such as laryngitis, pharyngitis, and pulmonary fibrosis. It also has been proposed that GERD might exacerbate asthma. These extraesophageal manifestations are challenging for patients and physicians because, although they may result from GERD, they may also be due to a host of other causes. Even in patients with established GERD, it can be difficult to establish that GERD is the cause of these extraesophageal problems.

There is no gold standard for the diagnosis of GERD. Thus, the diagnosis is based on a combination of symptom presentation, endoscopic evaluation of esophageal mucosa, reflux monitoring, and response to therapeutic intervention. Heartburn and regurgitation remain the most sensitive and specific symptoms for GERD, although not as reliable as one might believe. A well-performed but older systematic review found a variable sensitivity of heartburn and regurgitation for erosive esophagitis (EE) (30%–76%), with the specificity ranging from 62 to 96% (6). Most consensus statements and guidelines advocate a trial of therapy with a PPI as a diagnostic "test" in patients with the typical symptoms of heartburn and regurgitation, with the underlying assumption that a PPI response establishes the diagnosis of GERD. Although this a practical and efficient approach, it is

Table 1. Summary and strength of recommendations

	GRADE quality of evidence	GRADE strength of recommendation
Diagnosis of GERD		
For patients with classic GERD symptoms of heartburn and regurgitation who have no alarm symptoms, we recommend an 8-wk trial of empiric PPIs once daily before a meal.	Moderate	Strong
We recommend attempting to discontinue the PPIs in patients whose classic GERD symptoms respond to an 8-wk empiric trial of PPIs.	Low	Conditional
In patients with chest pain who have had adequate evaluation to exclude heart disease, objective testing for GERD (endoscopy and/or reflux monitoring) is recommended.	Low	Conditional
We do not recommend the use of a barium swallow solely as a diagnostic test for GERD.	Low	Conditional
We recommend endoscopy as the first test for evaluation of patients presenting with dysphagia or other alarm symptoms (weight loss and GI bleeding) and for patients with multiple risk factors for Barrett's esophagus.	Low	Strong
In patients for whom the diagnosis of GERD is suspected but not clear, and endoscopy shows no objective evidence of GERD, we recommend reflux monitoring be performed off therapy to establish the diagnosis.	Low	Strong
We suggest against performing reflux monitoring off therapy solely as a diagnostic test for GERD in patients known to have endoscopic evidence of LA grade C or D reflux esophagitis or in patients known to have long-segment Barrett's esophagus.	Low	Strong
GERD management		
We recommend weight loss in overweight and obese patients for improvement of GERD symptoms.	Moderate	Strong
We suggest avoiding meals within 2–3 hr of bedtime.	Low	Conditional
We suggest avoidance of tobacco products/smoking in patients with GERD symptoms.	Low	Conditional
We suggest avoidance of "trigger foods" for GERD symptom control.	Low	Conditional
We suggest elevating head of bed for nighttime GERD symptoms.	Low	Conditional
We recommend treatment with PPIs over treatment with H2RA for healing EE.	High	Strong
We recommend treatment with PPIs over H2RA for maintenance of healing for EE.	Moderate	Strong
We recommend PPI administration 30–60 min before a meal rather than at bedtime for GERD symptom control.	Moderate	Strong
For patients with GERD who do not have EE or Barrett's esophagus, and whose symptoms have resolved with PPI therapy, an attempt should be made to discontinue PPIs	Low	Conditional
For patients with GERD who require maintenance therapy with PPIs, the PPIs should be administered in the lowest dose that effectively controls GERD symptoms and maintains healing of reflux esophagitis.	Low	Conditional
We recommend against routine addition of medical therapies in PPI nonresponders.	Moderate	Conditional
We recommend maintenance PPI therapy indefinitely or antireflux surgery for patients with LA grade C or D esophagitis.	Moderate	Strong
We do not recommend baclofen in the absence of objective evidence of GERD.	Moderate	Strong
We recommend against treatment with a prokinetic agent of any kind for GERD therapy unless there is objective evidence of gastroparesis.	Low	Strong
We do not recommend sucralfate for GERD therapy except during pregnancy.	Low	Strong
We suggest on-demand/or intermittent PPI therapy for heartburn symptom control in patients with NERD.	Low	Conditional
Extraesophageal GERD symptoms		
We recommend evaluation for non-GERD causes in patients with possible extraesophageal manifestations before ascribing symptoms to GERD.	Moderate	Strong
We recommend that patients who have extraesophageal manifestations of GERD without typical GERD symptoms (e.g., heartburn and regurgitation) undergo reflux testing for evaluation before PPI therapy.	Moderate	Strong
For patients who have both extraesophageal and typical GERD symptoms, we suggest considering a trial of twice-daily PPI therapy for 8–12 wk before additional testing.	Low	Conditional
We suggest that upper endoscopy should not be used as the method to establish a diagnosis of GERD-related asthma, chronic cough, or LPR.	Low	Conditional

Table 1. (*continued*)

	GRADE quality of evidence	GRADE strength of recommendation
We suggest against a diagnosis of LPR based on laryngoscopy findings alone and recommend additional testing should be considered.	Low	Conditional
In patients treated for extraesophageal reflux disease, surgical or endoscopic antireflux procedures are only recommended in patients with objective evidence of reflux.	Low	Conditional
Refractory GERD		
We recommend optimization of PPI therapy as the first step in management of refractory GERD.	Moderate	Strong
We recommend esophageal pH monitoring (Bravo, catheter-based, or combined impedance-pH monitoring) performed OFF PPIs if the diagnosis of GERD has not been established by a previous pH monitoring study or an endoscopy showing long-segment Barrett's esophagus or severe reflux esophagitis (LA grade C or D).	Low	Conditional
We recommend esophageal impedance-pH monitoring performed ON PPIs for patients with an established diagnosis of GERD whose symptoms have not responded adequately to twice-daily PPI therapy.	Low	Conditional
For patients who have regurgitation as their primary PPI-refractory symptom and who have had abnormal gastroesophageal reflux documented by objective testing, we recommend consideration of antireflux surgery or TIF.	Low	Conditional
Surgical and endoscopic options for GERD		
We recommend antireflux surgery performed by an experienced surgeon as an option for long-term treatment of patients with objective evidence of GERD. Those who have severe reflux esophagitis (LA grade C or D), large hiatal hernias, and/or persistent, troublesome GERD symptoms who are likely to benefit most from surgery.	Moderate	Strong
We recommend consideration of MSA as an alternative to laparoscopic fundoplication for patients with regurgitation who fail medical management.	Moderate	Strong
We recommend consideration of RYGB as an option to treat GERD in obese patients who are candidates for this procedure and who are willing to accept its risks and requirements for lifestyle alterations.	Low	Conditional
Because data on the efficacy of radiofrequency energy (Stretta) as an antireflux procedure is inconsistent and highly variable, we cannot recommend its use as an alternative to medical or surgical antireflux therapies.	Low	Conditional
We suggest consideration of TIF for patients with troublesome regurgitation or heartburn who do not wish to undergo antireflux surgery and who do not have severe reflux esophagitis (LA grade C or D) or hiatal hernias >2 cm.	Low	Conditional

EE, erosive esophagitis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; H2RA, histamine-2-receptor antagonists; LA, Los Angeles; LPR, laryngopharyngeal reflux; MSA, magnetic sphincter augmentation; NERD, nonerosive reflux disease; PPI, proton pump inhibitor; TIF, transoral incisionless fundoplication; RYGB, Roux-en-Y gastric bypass.

limited by a pooled sensitivity of 78% and specificity of only 54% (using endoscopy and pH monitoring as the reference standard) based on a meta-analysis and prospective study (7,8).

Chest pain is commonly listed as a symptom of GERD. Similar to heartburn, a PPI trial has often been used for diagnosis of suspected GERD-related chest pain (9). However, a systematic review of PPI treatment of noncardiac chest pain found that symptom improvement with a PPI trial was effective only in patients with EE or abnormal pH monitoring (10). There was no significant response to PPIs compared with placebo when endoscopy and pH monitoring were normal, and the symptoms of chest pain and heartburn did not reliably predict a PPI response (11).

Atypical extraesophageal symptoms and conditions such as chronic cough, dysphonia, asthma, sinusitis, laryngitis, and dental erosions have been associated with GERD. However, these symptoms and conditions have poor sensitivity and specificity for the diagnosis of GERD. Diagnoses of GERD by extraesophageal symptoms alone or by their response to PPIs are unreliable because of poor sensitivity and specificity for GERD and not recommended (see additional discussion in the "Extraesophageal GERD" section below).

Barium radiography

Barium radiographs should not be used solely as a diagnostic test for GERD. The presence of reflux on a barium esophagram or upper GI series has poor sensitivity and specificity for GERD when compared with pH testing. In a recent prospective study, only about one-half of patients with abnormal reflux on a barium study were found to have abnormal pH monitoring (12,13). The finding of barium reflux above the thoracic inlet with or without provocative maneuvers (including the water siphon test) somewhat increases the sensitivity for reflux, but not sufficiently for barium esophagram to be recommended as a diagnostic test for GERD (14).

Table 2. Key concept statements

Diagnosis of GERD
We do not recommend HRM solely as a diagnostic test for GERD.
GERD management
There is conceptual rationale for a trial of switching PPIs for patients who have not responded to one PPI. For patients who have not responded to one PPI, more than one switch to another PPI cannot be supported.
Use of the lowest effective dose is recommended and logical but must be individualized. One area of controversy relates to abrupt PPI discontinuation and potential rebound acid hypersecretion, resulting in increased reflux symptoms. Although this has been demonstrated to occur in healthy controls, strong evidence for an increase in symptoms after abrupt PPI withdrawal is lacking.
Extraesophageal GERD
Although GERD may be a contributor to extraesophageal symptoms in some patients, careful evaluation for other causes should be considered for patients with laryngeal symptoms, chronic cough, and asthma.
Diagnosis, evaluation, and management of potential extraesophageal symptoms of GERD is limited by lack of a gold-standard test, variable symptoms, and other disorders which may cause similar symptoms
Endoscopy is not sufficient to confirm or refute the presence of extraesophageal GERD.
Because of difficulty in distinguishing between patient with laryngeal symptoms and normal controls, salivary pepsin testing is not recommended for evaluation of patients with extraesophageal reflux symptoms
For patients whose extraesophageal symptoms have not responded to a trial of twice-daily PPIs, we recommend upper endoscopy, ideally off PPIs for 2–4 wk. If endoscopy is normal, consider reflux monitoring. If EGD shows EE, that does not confirm that the extraesophageal symptoms are from GERD. Patients still may need pH-impedance testing
For patients with extraesophageal symptoms, we do not routinely recommend oropharyngeal or pharyngeal pH monitoring.
Refractory GERD
It is important to stop PPI therapy in patients whose off-therapy reflux testing is negative, unless another indication for continuing PPIs is present. In 1 study, 42% of patients reported continuing PPI treatment after a negative evaluation for refractory GERD, which included negative endoscopy and pH-impedance monitoring [2].
Esophageal manometry should be considered as part of the evaluation for patients with refractory GERD in patients with a normal endoscopy and pH monitoring study and for patients being considered for surgical or endoscopic treatment.
If not already performed off PPIs, we recommend diagnostic upper endoscopy with esophageal biopsies after discontinuing PPI therapy, ideally for 2 to 4 wk
For patients with PPI-refractory symptoms who have a normal pH monitoring test OFF PPIs or a normal impedance-pH monitoring test ON PPIs (including a negative SI and SAP), we recommend discontinuation of PPIs unless there is an indication for PPI therapy other than the refractory symptoms.
Surgical and endoscopic therapy
We recommend HRM before antireflux surgery or endoscopic therapy to rule out achalasia and absent contractility. For patients with ineffective esophageal motility, HRM should include provocative testing to identify contractile reserve (e.g., multiple rapid swallows).
We recommend a careful evaluation and caution before proceeding with invasive therapy for patients with PPI-refractory GERD symptoms other than regurgitation.
Before performing invasive therapy for GERD, a careful evaluation is required to ensure that GERD is present and as best as possible determine is the cause of the symptoms to be addressed by the therapy, to exclude achalasia (which can be associated with symptoms such as heartburn and regurgitation that can be confused with GERD), and to exclude conditions that might be contraindications to invasive treatment such as absent contractility.
Long-term PPI issues
Regarding the safety of long-term PPI usage for GERD, we suggest that patients should be advised as follows: "PPIs are the most effective medical treatment for GERD. Some medical studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. Those studies have flaws, are not considered definitive, and do not establish a cause-and-effect relationship between PPIs and the adverse conditions. High-quality studies have found that PPIs do not significantly increase the risk of any of these conditions except intestinal infections. Nevertheless, we cannot exclude the possibility that PPIs might confer a small increase in the risk of developing these adverse conditions. For the treatment of GERD, gastroenterologists generally agree that the well-established benefits of PPIs far outweigh their theoretical risks."
Switching PPIs can be considered for patients who experience minor PPI side effects including headache, abdominal pain, nausea, vomiting, diarrhea, constipation, and flatulence.
For patients with GERD on PPIs who have no other risk factors for bone disease, we do not recommend that they raise their intake of calcium or vitamin D or that they have routine monitoring of bone mineral density.

Table 2. (*continued*)

For patients with GERD on PPIs who have no other risk factors for vitamin B12 deficiency, we do not recommend that they raise their intake of vitamin B12 or that they have routine monitoring of serum B12 levels.
For patients with GERD on PPIs who have no other risk factors for kidney disease, we do not recommend that they have routine monitoring of serum creatinine levels.
For patients with GERD on clopidogrel who have LA grade C or D esophagitis or whose GERD symptoms are not adequately controlled with alternative medical therapies, the highest quality data available suggest that the established benefits of PPI treatment outweigh their proposed but highly questionable cardiovascular risks.
PPIs can be used to treat GERD in patients with renal insufficiency with close monitoring of renal function or consultation with a nephrologist.

EE, erosive esophagitis; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; LA, Los Angeles; PPI, proton pump inhibitor; SAP, symptom association probability; SI, symptom index.

Endoscopy

Upper endoscopy is the most widely used objective test for evaluating the esophageal mucosa. For patients with GERD symptoms who also have alarm symptoms such as dysphagia, weight loss, bleeding, vomiting, and/or anemia, endoscopy should be performed as soon as feasible. The endoscopic findings of EE and Barrett's esophagus are specific for the diagnosis of GERD. The LA classification of EE is the most widely used and validated scoring system (15). Recent expert consensus statements concluded that LA grade A EE is not sufficient for a definitive diagnosis of GERD because it is not reliably differentiated from normal (16,17). LA grade B EE can be diagnostic of GERD in the presence of typical GERD symptoms and PPI response, whereas LA grade C is virtually always diagnostic of GERD. In outpatients, LA grade D EE is a manifestation of severe GERD, but LA grade D EE might not be a reliable index of GERD severity in hospitalized patients. The finding of any Barrett's esophagus segment >3 cm with intestinal metaplasia on biopsy is diagnostic of GERD and obviates the need for pH testing merely to confirm that diagnosis. In patients with LA grade C and D EE, endoscopy is recommended after PPI treatment to ensure healing and to evaluate for Barrett's esophagus, which can be difficult to detect when severe EE is present.

For patients having endoscopy for typical GERD symptoms, normal mucosa is the most common finding. There are limited data on the frequency of finding EE in patients undergoing endoscopy while taking PPIs, but, because PPIs are highly effective for healing EE, underlying EE clearly can be missed in this setting. Consequently, a diagnosis of nonerosive reflux disease (NERD) should only be made if endoscopy is performed off PPIs. To maximize the yield of GERD diagnosis and assess for EE, diagnostic endoscopy should ideally be performed after PPIs have been stopped for 2 weeks and perhaps as long as 4 weeks if possible. In a small prospective study assessing relapse of EE in patients with LA grade C EE that was healed with PPIs, discontinuation of PPI therapy led to return of EE in as little as 1 week (18). Stopping PPIs for 2–4 weeks also will facilitate a diagnosis of EoE, which is a diagnostic consideration when endoscopy is performed for patients with symptoms that are believed to be due to GERD but are not eliminated by PPIs (19). Although esophageal biopsies have little value as a diagnostic test for GERD, they are required to establish a diagnosis of EoE. Because PPIs can eliminate the endoscopic and histologic features of EoE, the diagnosis of EoE cannot be excluded if endoscopy is performed while the patient is taking PPIs (19). Patients should be advised that they can take antacids for symptom relief during this period of 2–4 weeks off PPIs. Some patients will not be able to tolerate discontinuing their PPI therapy, but the diagnostic advantages discussed above warrant an attempt at stopping PPIs before performing diagnostic endoscopy for GERD.

Esophageal manometry

HRM can be used to assess motility abnormalities associated with GERD, but HRM is not alone a diagnostic test for GERD. Weak lower esophageal sphincter (LES) pressure and ineffective esophageal motility often accompany severe GERD, but no manometric abnormality is specific for GERD. For esophageal impedance-pH monitoring, HRM is used to locate the LES for positioning of transnasal pH-impedance catheters. HRM also has a role in the evaluation of patients considering surgical or endoscopic antireflux procedures, primarily to evaluate for achalasia. Patients with achalasia can have heartburn and regurgitation that are mistaken for GERD symptoms, and antireflux procedures performed for such a mistaken diagnosis of GERD can result in devastating dysphagia. Thus, HRM should ideally be performed in all patients before any antireflux procedure. Although esophageal manometry has been proposed as a means to "tailor" antireflux operations, with Nissen (complete) fundoplication reserved for patients with normal peristalsis and partial fundoplication used for those with ineffective esophageal motility, studies on this issue have not supported the efficacy of this approach. Nevertheless, absent contractility is for most a contraindication to fundoplication. Newer developments in HRM include physiologic assessment of esophagogastric junction morphology and provocative testing with multiple rapid swallows or the rapid drink challenge. In patients undergoing surgical treatment of GERD, reduced contractile reserve documented by multiple rapid swallows on HRM is associated with postoperative dysphagia (20). More data are needed to clarify the role of altered motility on outcomes after magnetic sphincter augmentation (MSA) and transoral incisionless fundoplication (TIF). Until those are forthcoming, a preoperative HRM is recommended. HRM is part of the diagnostic work up for patients unresponsive to PPIs when an etiology for symptoms cannot be demonstrated by impedance-pH monitoring and in patients with noncardiac chest pain especially those not responsive to a PPI trial to assess for motility abnormalities.

Reflux monitoring

Ambulatory reflux monitoring (pH or impedance-pH) allows for assessment of esophageal acid exposure to establish or refute a diagnosis of GERD and for correlating symptoms with reflux episodes using the symptom index (SI) or symptom association probability (SAP). The main methods of reflux testing include a wireless telemetry capsule (Bravo Reflux Capsule; Medtronic, Minneapolis, MN) attached to the esophageal mucosa during endoscopy and transnasal catheter-based testing, and there are strengths and weaknesses to each approach. With transnasally positioned pH and pH/impedance
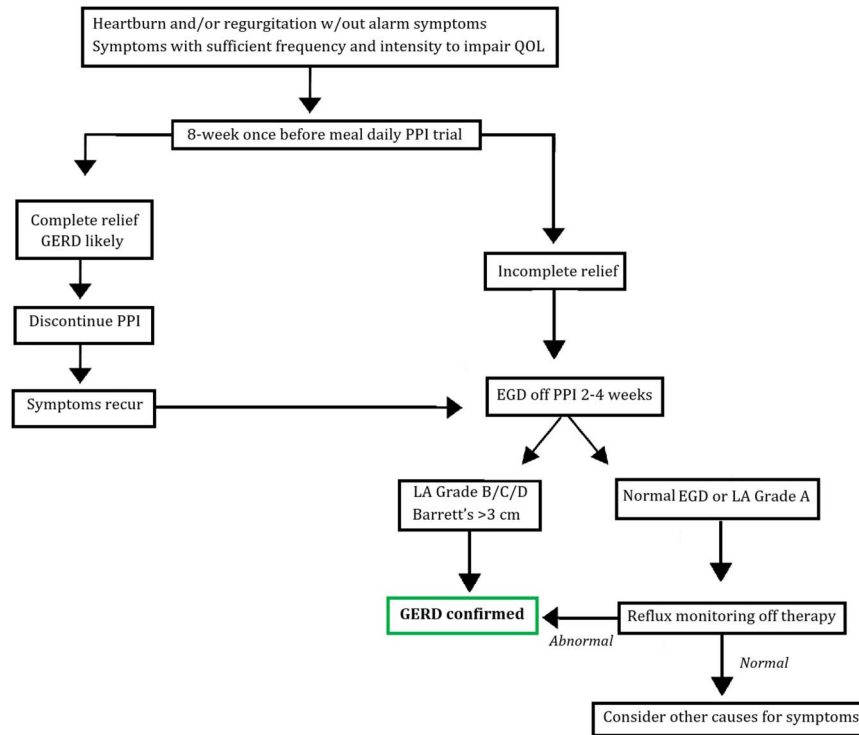
Figure 1. Diagnosis of GERD. EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; LA, Los Angeles; PPI, proton pump inhibitor; QOL, quality of life.

catheters, the monitoring period generally is limited to 24 hours, while wireless pH telemetry capsule monitoring can last from 48 to 96 hours. In addition, the capsule avoids the physical discomfort and embarrassment of a transnasal catheter, and so, patients are more likely to carry on normal daily activities during capsule pH monitoring (21,22). There is no capsule system available for impedance monitoring, which requires a transnasal catheter. Dual-pH sensor transnasal catheters and a hypopharyngeal pH probe are also available to document acid reflux into the proximal esophagus and oropharynx, but the utility of these techniques is highly questionable with studies reporting widely disparate results (see "extraesophageal" section). Several factors are assessed during reflux testing, including acid exposure time, number of reflux events, and symptom correlation. Impedance-pH testing also allows for measurement of weakly acidic and nonacid reflux, assessment of bolus clearance, and extent of proximal reflux. Reflux symptom association on impedance-pH testing may help predict symptom response to therapy and may help in diagnosing reflux hypersensitivity (23). With both wireless capsule and catheter-based reflux tests, the most consistently reliable variables include the total acid exposure time and the composite DeMeester score.

The relationship between symptoms and reflux events can be assessed using the SI or SAP. To calculate SI, the total number of reflux episodes associated with symptom episodes is divided by the total number of symptom episodes during the entire monitoring period; an SI $\geq$ 50% is considered positive. To determine the SAP, the 24-hour monitoring period is divided into 720 two-minute increments, and each increment is evaluated for the occurrence of reflux and symptom episodes. A Fisher exact test is performed to determine a P value for the probability that reflux and symptom events are randomly distributed, and the SAP is determined by subtracting the calculated P value from 1 and multiplying the remainder by 100%; an SAP $>$ 95% is considered positive. The validity of both of these indices has been questioned, and

neither has been demonstrated superior to the other for clinical purposes. The sensitivity and specificity of reflux monitoring is high in patients with GERD with EE, although perhaps not as accurate in those with a normal endoscopy. Impedance monitoring that enables detection of weakly acidic and nonacidic reflux has been shown to be useful in identifying patients with reflux hypersensitivity who might respond to antireflux surgery (24).

An issue that frequently arises is whether esophageal pH monitoring should be performed on or off PPI therapy. It is generally recommended to monitor after PPIs are stopped for 7 days if the diagnosis of GERD is not clear and before antireflux surgery or endoscopic therapy for GERD to document abnormal acid reflux (17). This recommendation includes testing with either the telemetry capsule (48–96 hours) or impedance-pH catheter. Reflux monitoring while on PPI therapy is suggested in patients who have had the diagnosis of GERD established by previous objective evidence (i.e., EE, Barrett's esophagus, and previous pH testing off PPI) but who have symptoms potentially reflux-related that have not responded to PPIs. In these patients, impedance/pH testing is recommended to document reflux hypersensitivity for weakly acidic or nonacidic reflux and for acid reflux. Figure 1 outlines an overall approach to the diagnosis of GERD.

Diagnosis of GERD in pregnancy

Approximately two-thirds of pregnant women experience heartburn, which can begin in any trimester (25). Most patients do not have a previous diagnosis of GERD (26), although a history of GERD may increase the likelihood of GERD occurring during pregnancy. Despite its frequent occurrence during pregnancy, heartburn usually resolves after delivery (27). Pregnancy and the amount of weight gain during pregnancy are risk factors for frequent GERD symptoms 1 year after delivery (27). Heartburn is the only GERD symptom that has been studied in pregnancy, and

the diagnosis of GERD is almost always symptom-based. Endoscopy and pH monitoring are rarely needed.

New developments

A recently approved device for evaluation of GERD uses a catheter-based balloon lined by sensors that measure mucosal impedance during endoscopy. This technique has shown promise for differentiating GERD from EoE and may develop to be a useful adjunct to endoscopy in the diagnosis of GERD (28).

GERD MEDICAL MANAGEMENT

Recommendations

1. We recommend weight loss in overweight and obese patients for improvement of GERD symptoms (strong recommendation, moderate level of evidence).
2. We suggest avoiding meals within 2–3 hours of bedtime (conditional recommendation, low level of evidence).
3. We suggest avoidance of tobacco products/smoking in patients with GERD symptoms (conditional recommendation, low level of evidence).
4. We suggest avoidance of "trigger foods" for GERD symptom control (conditional recommendation, low level of evidence).
5. We suggest elevating head of bed for nighttime GERD symptoms (conditional recommendation, low level of evidence).
6. We recommend treatment with PPIs over treatment with histamine-2-receptor antagonists (H2RA) for healing EE (strong recommendation, high level of evidence).
7. We recommend treatment with PPIs over H2RA for maintenance of healing from EE (strong recommendation, moderate level of evidence).
8. We recommend PPI administration 30–60 minutes before a meal rather than at bedtime for GERD symptom control (strong recommendation, moderate level of evidence).
9. For patients with GERD who do not have EE or Barrett's esophagus, and whose symptoms have resolved with PPI therapy, an attempt should be made to discontinue PPIs or to switch to on-demand therapy in which PPIs are taken only when symptoms occur and discontinued when they are relieved (conditional recommendation, low level of evidence).
10. For patients with GERD who require maintenance therapy with PPIs, the PPIs should be administered in the lowest dose that effectively controls GERD symptoms and maintains healing of reflux esophagitis (conditional recommendation, low level of evidence).
11. We recommend against routine addition of medical therapies in PPI nonresponders (conditional recommendation, moderate level of evidence).
12. We recommend maintenance PPI therapy indefinitely or antireflux surgery for patients with LA grade C or D esophagitis (strong recommendation, moderate level of evidence).
13. We do not recommend baclofen in the absence of objective evidence of GERD (strong recommendation, moderate level of evidence).
14. We recommend against treatment with a prokinetic agent of any kind for GERD therapy unless there is objective evidence of gastroparesis (strong recommendation, low level of evidence).
15. We do not recommend sucralfate for GERD therapy except during pregnancy (strong recommendation, low level of evidence).
16. We suggest on-demand or intermittent PPI therapy for heartburn symptom control in patients with NERD (conditional recommendation, low level of evidence).

Key concepts

1. There is conceptual rationale for a trial of switching PPIs for patients who have not responded to one PPI. For patients who have not responded to one PPI, more than one switch to another PPI cannot be supported.
2. Use of the lowest effective PPI dose is recommended and logical but must be individualized. One area of controversy relates to abrupt PPI discontinuation and potential rebound acid hypersecretion, resulting in increased reflux symptoms. Although this has been demonstrated to occur in healthy controls, strong evidence for an increase in symptoms after abrupt PPI withdrawal is lacking.

Management of GERD requires a multifaceted approach, taking into account the symptom presentation, endoscopic findings, and likely physiological abnormalities. Management decisions may differ depending on hiatal hernia type and size, on the presence of EE and/or Barrett's esophagus, body mass index (BMI), and on accompanying physiologic abnormalities such as gastroparesis or ineffective motility with absence of contractile reserve. Medical management includes lifestyle modifications and pharmacologic therapy, principally with medications that reduce gastric acid secretion. Surgical and endoscopic options are discussed in other sections. Nonpharmacologic lifestyle modifications include recommendations for diet modification (content and timing), body positioning with meals and while sleeping, and weight management (Table 3).

Diet and lifestyle changes

Common recommendations include weight loss for overweight patients, elevating the head of the bed, tobacco and alcohol cessation, avoidance of late night meals and bedtime snacks, staying upright during and after meals, and cessation of foods that potentially aggravate reflux symptoms such as coffee, chocolate, carbonated beverages, spicy foods, acidic foods such as citrus and tomatoes, and foods with high fat content (29). Supporting data for these recommendations are limited and variable, often involving only small and uncontrolled studies, and rarely as the only intervention, making interpretation and definitive recommendations difficult. However, multiple studies, including several randomized controlled trials (RCTs), have demonstrated improvement in nocturnal GERD symptoms and nocturnal esophageal acid exposure with head of bed elevation or sleeping on a wedge. Also, compared with lying left-side down, lying right-side down increases nocturnal reflux and reflux after meals, presumably because right-sided recumbency places the EGJ in a dependent position relative to the pool of gastric contents that favors reflux (30,31). Thus, patients might be advised to avoid sleeping right-side down (32–35).

Several studies have evaluated the effects of various foods on LES pressure to try to determine which items might lead to GERD. In laboratory studies, coffee, caffeine, citrus, and spicy food had little to no effect on LES pressure (36,37). However, some of these items might have irritant effects that could evoke GERD symptoms without influencing reflux. Alcohol consumption, tobacco smoking, chocolate, peppermint, and high-fat foods do reduce LES pressure in the laboratory, but few studies document the benefits of avoiding these foods and practices. Smoking cessation was shown to improve GERD symptoms in a large cohort study (38). Patients in a smoking cessation study had GERD symptoms measured by validated questionnaire, and those who successfully quit smoking for a year had 44%

Table 3. Recommendations based on results of a review of studies involving lifestyle modifications

Lifestyle modification	Strength of scientific evidence	Pathophysiologically conclusive?	Recommendable?
Avoid fatty meals	Equivocal	Equivocal	Yes
Avoid carbonated beverages	Moderate	Yes	Yes
Select decaffeinated beverages	Equivocal	Equivocal	Not generally
Avoid citrus	Weak	Yes	Yes, if citrus triggers symptoms
Eat smaller meals	Weak	Yes	Yes
Lose weight	Equivocal	Equivocal	Yes[a]
Avoid alcoholic beverages	Weak	Mechanisms not understood; different alcoholic beverages have different effects	Not generally
Stop smoking	Weak	Yes	Yes[a]
Avoid excessive exercise	Weak	Yes	Yes
Sleep with head elevated	Equivocal	Equivocal	Yes
Sleep on the left side	Unequivocal	Yes	Yes

[a]Obesity and smoking seem to be risk factors for cancer of the distal esophagus.

improvement in GERD symptoms, compared with 18% in those who continued to smoke (39).

A recent article, using data collected from the prospective Nurses' Health Study, evaluated women without a known history of GERD for the impact of coffee, tea, soda, milk, water, and juice on reflux symptoms. Six servings of coffee, tea, and soda were associated with increased reflux symptoms compared with zero servings per day. By contrast, milk and juice were not associated with increased reflux symptoms, despite the acidic nature of some of these beverages (40). Substituting water for 2 servings of coffee, tea, and soda was associated with a decrease in GERD symptoms, suggesting that substitution of water for these beverages might be helpful in the management of GERD.

The timing of food intake can also affect GERD symptoms. A short interval (<3 hours) between eating and bedtime or lying supine is associated with increased GERD symptoms and need for medication (41). Weight gain has been associated with new onset of GERD symptoms (42), even in those with a normal BMI at baseline. Obesity increases the risk of GERD, possibly because of a combination of eating a diet high in fat and other foods that promote reflux, increased intra-abdominal pressure that promotes reflux because of increased intra-abdominal fat, and physiologic changes induced by products of visceral fat (43). Several studies have examined the role of weight and weight loss on GERD. A population-based study in Norway assessed weight and GERD symptoms at baseline and 10 years later and identified a dose-dependent improvement in GERD symptoms with weight loss (44). Prospective and cohort studies also have shown improvement in GERD with weight loss. One study documented a 40% reduction in frequent GERD symptoms in women who reduced their BMI by 3.5 or more compared with controls (45). A meta-analysis suggests that weight loss in overweight patients, avoidance of eating before going to sleep, and smoking cessation are effective in relief of GERD symptoms (46).

Medications
The backbone of pharmacologic therapy for GERD are medications that are directed at neutralization or reduction of gastric acid. Agents in this class include antacids, H2RA, and PPIs. Antacids are used exclusively for on-demand symptom relief with little evidence to favor 1 type over another. Studies with an alginic acid preparation manufactured in the United Kingdom suggest potential efficacy in symptom relief compared with other products, but alginate content of preparations sold in other countries is variable (47).

Proton pump inhibitors
PPIs are the most commonly prescribed medication based on ample data demonstrating consistently superior heartburn and regurgitation relief, as well as improved healing compared with H2RAs. A meta-analysis (published when only 2 PPIs were available) provides important insight into PPI efficacy. PPIs showed a significantly faster healing rate (12%/week) vs H2RAs (6%/week), and faster, more complete heartburn relief (11.5%/week) vs H2RAs (6.4%/week) (48,49).

Studies on GERD treatment typically last only 8–12 weeks, in part because symptom relief and healing seem to peak in that time frame. The healing rates of EE are not linear; thus, clinicians and patients need to understand that symptom relief and healing may not be rapid. PPIs are associated with a greater rate of "complete" symptom relief (usually assessed at 4 weeks) in patients with EE (~70%–80%) compared with patients with so-called NERD in which symptom relief approximates 50%–60% (50). Trials in patients with NERD are based on symptoms of frequent heartburn and the absence of erosions on an index endoscopy without objective documentation of GERD by reflux monitoring. There are likely many patients included in NERD who have functional heartburn and thus unlikely to respond to PPIs.

Meta-analyses suggest that overall GERD symptom relief and healing rates differ little among the 7 available PPIs, despite studies demonstrating differences in pH control. A meta-analysis examining efficacy of different PPIs for healing of EE included 10 studies (15,316 patients) (51). At 8 weeks, there was a 5% (relative risk [RR], 1.05; 95% confidence interval [CI], 1.02–1.08) relative increase in the probability of healing of EE with esomeprazole, yielding an absolute risk reduction of 4% and number needed to treat of 25, a number unlikely to be clinically meaningful. Although all the PPIs are effective for healing reflux esophagitis when given in their standard dosages, there are wide variations in the acid-suppression potency of the different PPI preparations. If relative acid-suppression potencies of individual PPIs (based on their effects on mean 24-hour intragastric pH) are standardized to omeprazole to yield "omeprazole equivalents" (OEs, with

omeprazole having an OE of 1.00), the relative potencies of standard-dose pantoprazole, lansoprazole, omeprazole, esomeprazole, and rabeprazole have been estimated at 0.23, 0.90, 1.00, 1.60, and 1.82 OEs, respectively (52,53).

PPIs can bind only to proton pumps that are actively secreting acid. Because meals stimulate proton pump activity, enteric-coated PPIs control intragastric pH best when given before a meal (30–60 minutes before breakfast for once-daily dosing and 30–60 minutes before breakfast and dinner for twice-daily dosing (54,55)). Bedtime dosing is discouraged because this is less effective than a predinner dose in acid control (56).

Dexlansoprazole, a dual delayed release PPI, in which first absorption is in the duodenum, then partially further down the small bowel, seems to have similar efficacy in pH control regardless of meal timing. An omeprazole-sodium bicarbonate combination that is not enteric-coated provides good control of intragastric pH in the first 4 hours of sleep when dosed at bedtime (57). There seems to be a wide variation in individual intragastric pH control between PPIs, a rationale for considering switching PPIs in patients with incomplete response (58). In a study of 282 patients with persistent heartburn on lansoprazole 30 mg once daily who were randomized either to double the dose of lansoprazole or to switch to esomeprazole 40 mg once daily, the 2 strategies were equally effective, with approximately 55% of patients in both groups experiencing a decrease in the percentage of heartburn-free days (59). Studies suggest that genetic differences in CYP2C19 metabolism affect PPI response; however, genetic testing in this regard has no established role in practice. If one is considering a PPI switch, changing to a PPI that does not rely on CYP2C19 for primary metabolism (rabeprazole) might be considered.

Maintenance PPI therapy should be administered for patients with GERD complications including severe EE (LA grade C or D) and Barrett's esophagus (60). For patients without EE or Barrett's esophagus who continue to have symptoms when PPI therapy is discontinued, consideration can be given to on-demand therapy in which PPIs are taken only when symptoms occur and discontinued when they are relieved (61,62). Two-thirds of patients with non-erosive disease responsive to PPIs will demonstrate symptomatic relapse when PPIs are stopped. With LA grade C esophagitis, nearly 100% will relapse within 6 months (63). Recurrence of EE after discontinuation can occur in as little as 1–2 weeks, particularly in patients with previous LA grade C EE (18). Patients with LA grade C or D EE should remain on long-term PPI therapy to maintain healing.

In some cases, patients with NERD and otherwise non-complicated GERD can be managed successfully with on-demand or intermittent PPI therapy. In 1 RCT, 83% of patients with NERD randomized to 20 mg of omeprazole on demand were in remission at 6 months compared with 56% of patient on placebo (64). In a systematic review of RCTs comparing on-demand PPI vs placebo, symptom-free days for patients with NERD in the on-demand arm were equivalent to rates for patients on continuous PPI therapy, and both on-demand and continuous PPIs were superior to placebo. On-demand PPI therapy was not better than continuous PPI therapy for patients with EE. Step-down therapy to H2RAs is another acceptable option for management, particularly in patients with NERD (65,66).

Use of the lowest effective dose is recommended and logical but must be individualized. One area of controversy relates to abrupt PPI discontinuation and potential rebound acid hyper-secretion, resulting in increased reflux symptoms. Although rebound acid hypersecretion has been demonstrated to occur in healthy controls, strong evidence for an increase in symptoms after abrupt PPI withdrawal is lacking (67–69).

H2RA taken at bedtime

Medical options for patients with GERD with incomplete symptom response on PPI therapy are limited. The addition of bedtime H2RA has been suggested for patients on PPIs with persistent nocturnal symptoms. This approach gained popularity after several studies demonstrated improved overnight intra-gastric pH control with the addition of an H2RA (70), although a well-performed study demonstrated loss of pH control (tachy-phylaxis) after a month of bedtime H2RA therapy (71). Based on these data, use of a bedtime H2RA may be beneficial if dosed on an as-needed basis for patients with nocturnal symptoms and for patients with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment.

Prokinetics

There are limited data on the use of prokinetic agents for patients with GERD. Metoclopramide has been shown to increase LES pressure, enhance esophageal peristalsis, and augment gastric emptying. However, data on its efficacy in GERD are scant, and significant adverse events have been reported with long-term and high-dose metoclopramide use, including central nervous system side effects such as drowsiness, agitation, irritability, depression, dystonic reactions, and tardive dyskinesia (72,73). Thus, we do not recommend using metoclopramide solely for the treatment of GERD. Prucalopride, a 5 HT agonist US Food and Drug Administration (FDA)-approved for treatment of constipation, was shown in 1 off-label use study to improve gastric emptying and reduce esophageal acid exposure in patients with GERD. In the future, this may be a potential add-on therapy for patients with GERD on PPIs found to have delayed gastric emptying (74).

Baclofen

Baclofen, a GABA^B agonist, reduces the transient LES relaxations that enable reflux episodes. Baclofen decreases the number of postprandial acid and nonacid reflux events, nocturnal reflux activity, and belching episodes (75–77). A trial of baclofen at a dosage of 5–20 mg 3 times a day can be considered in patients with objective documentation of continued symptomatic reflux despite optimal PPI therapy. Short-term RCTs have demonstrated symptomatic improvement with baclofen (75–77). A randomized, placebo-controlled trial of medical therapy (including baclofen) vs antireflux surgery for PPI-refractory heartburn found no significant benefit for baclofen compared with placebo at 1 year, but the study was not sufficiently powered to detect a small but potentially important effect for baclofen (24). Usage is limited by side effects of dizziness, somnolence, and constipation.

Sucralfate

Sucralfate is a mucosal protective agent, but few data document its efficacy in GERD. Limited studies have suggested similar efficacy to H2RAs, but there are no comparative data to PPIs nor any combination studies with these agents. Sucralfate is largely un-absorbed and has no systemic toxicity. There is little to recommend for this agent in GERD outside of pregnancy.

Treatment of GERD during pregnancy

A small RCT found that sucralfate was superior to dietary and lifestyle modifications for relieving heartburn and regurgitation in pregnant women (78). Approximately two-thirds of pregnant women experience heartburn. It has been recommended that treatment of GERD during pregnancy should start with lifestyle

modifications. When lifestyle modifications fail, antacids (aluminum-, calcium-, or magnesium-containing), alginates, and sucralfate are the first-line therapeutic agents. All histamine H2-blockers are FDA category B, and all PPIs are FDA category B except omeprazole, which is FDA category C.

EXTRAESOPHAGEAL GERD SYMPTOMS

The below recommendations for the diagnosis for extra-esophageal GERD are also illustrated in Figure 2.

Recommendations

1. We recommend evaluation for non-GERD causes in patients with possible extraesophageal manifestations before ascribing symptoms to GERD (strong recommendation, moderate level of evidence).
2. We recommend that patients who have extraesophageal manifestations of GERD without typical GERD symptoms (e.g., heartburn and regurgitation) undergo reflux testing for evaluation before PPI therapy (strong recommendation, moderate level of evidence).
3. For patients who have both extraesophageal and typical GERD symptoms, we suggest considering a trial of twice-daily PPI therapy for 8–12 weeks before additional testing (conditional recommendation, low level of evidence).
4. We suggest that upper endoscopy should not be used as the method to establish a diagnosis of GERD-related asthma, chronic cough, or laryngopharyngeal reflux (LPR) (conditional recommendation, low level of evidence).
5. We suggest against a diagnosis of LPR based on laryngoscopy findings alone and recommend additional testing should be considered (conditional recommendation, low level of evidence).
6. In patients treated for extraesophageal reflux disease, surgical or endoscopic antireflux procedures are only recommended in patients with objective evidence of reflux (conditional recommendation, low level of evidence).

Key concepts

1. Although GERD may be a contributor to extraesophageal symptoms in some patients, careful evaluation for other causes should be considered for patients with laryngeal symptoms, chronic cough, and asthma.
2. Diagnosis, evaluation, and management of potential extraesophageal symptoms of GERD is limited by lack of a gold-standard test, variable symptoms, and other disorders which may cause similar symptoms.
3. Because of difficulty in distinguishing between patient with laryngeal symptoms and normal controls, salivary pepsin testing is not recommended for evaluation of patients with extraesophageal reflux symptoms.
4. For patients whose extraesophageal symptoms have not responded to a trial of twice-daily PPIs, we recommend upper endoscopy, ideally off PPIs for 2–4 weeks. If endoscopy is normal, consider reflux monitoring. Demonstration of EE by endoscopy establishes a diagnosis of GERD, but does not confirm that GERD is the cause of the extraesophageal symptoms. Confirmation may require pH/impedance testing.
5. For patients with extraesophageal symptoms, we do not routinely recommend oropharyngeal or pharyngeal pH monitoring.

Numerous extraesophageal symptoms and conditions have been attributed to GERD, including chronic cough, throat-clearing, hoarseness, globus, asthma, and laryngitis. These are vexing for patients as well as physicians because the symptoms ascribed to extraesophageal GERD are often nonspecific and overlap with other disorders. Evaluation by otorhinolaryngology, allergy, and pulmonary specialists should be considered in these patients, depending on the constellation of symptoms. Currently available diagnostic tools to establish GERD as the cause of extraesophageal symptoms have substantial limitations. PPI treatment is relied on as both a diagnostic tool and treatment for extraesophageal GERD symptoms, but is often ineffective, and prolonged treatment trials with PPIs may delay diagnosis and care for patients with nonreflux laryngeal and pulmonary disorders.

Symptoms

The association between GERD and extraesophageal symptoms has been examined in multiple studies. In a case-control study of veterans, patients with esophagitis or esophageal strictures were more likely to have a diagnosis of laryngitis (odds ratio [OR] 2.01), aphonia (OR 1.81), asthma (OR 1.51), and pharyngitis (OR 1.48) compared with control patients (79). In a US survey study, 26% of patients reported both GERD and laryngeal symptoms (80). Of this group with both GERD and laryngeal complaints, 38% reported voice disorders and 44% had occasional breathing difficulties. Some studies have suggested that chronic cough may be due to GERD in 21%–41% of cases (81).

However, because of the wide variety of causes of chronic cough, the American College of Chest Physicians guideline for evaluation of chronic cough suggests looking for other sources before attributing chronic cough to GERD (82).

GERD may also have a role in asthma, with 1 systematic review of 28 studies identifying GERD symptoms in 59% of patients with asthma and abnormal pH testing in 51% (83). However, data from several RCTs suggest that PPI treatment is ineffective for many patients with asthma, which brings in to question the role of acid reflux in asthma symptoms (84,85).

Endoscopy

Endoscopy is frequently used for assessing classic symptoms of GERD, such as heartburn and regurgitation, but its role in assessment of extraesophageal GERD symptoms is less clear. In patients with extraesophageal GERD symptoms, the reported frequency of EE ranges from 18% to 52% (86,87). However, the presence of EE does not confirm GERD as a cause of extraesophageal symptoms because EE has been found in 16% of patients with no typical or extraesophageal GERD symptoms in a general population who were undergoing periodic health checkup (88). Nevertheless, if LA grade C or D EE is present, this establishes a diagnosis of severe GERD and justifies a trial of PPI therapy.

Laryngoscopy

Laryngoscopy performed by an otorhinolaryngologist (ENT) is commonly used to assess for signs of extraesophageal GERD, in particular, LPR. Findings on laryngoscopy that are associated with reflux include posterior commissure hypertrophy, laryngeal and arytenoid inflammation, vocal cord edema, and endolaryngeal mucus. Several scoring systems have been developed for grading the laryngoscopic findings, the most common of which is the reflux finding score (RFS) (89). However, correlation between symptoms, laryngoscopic findings, and other objective testing such as pH and pH-impedance monitoring is low. In a systematic review evaluating different reported signs of LPR and relevant
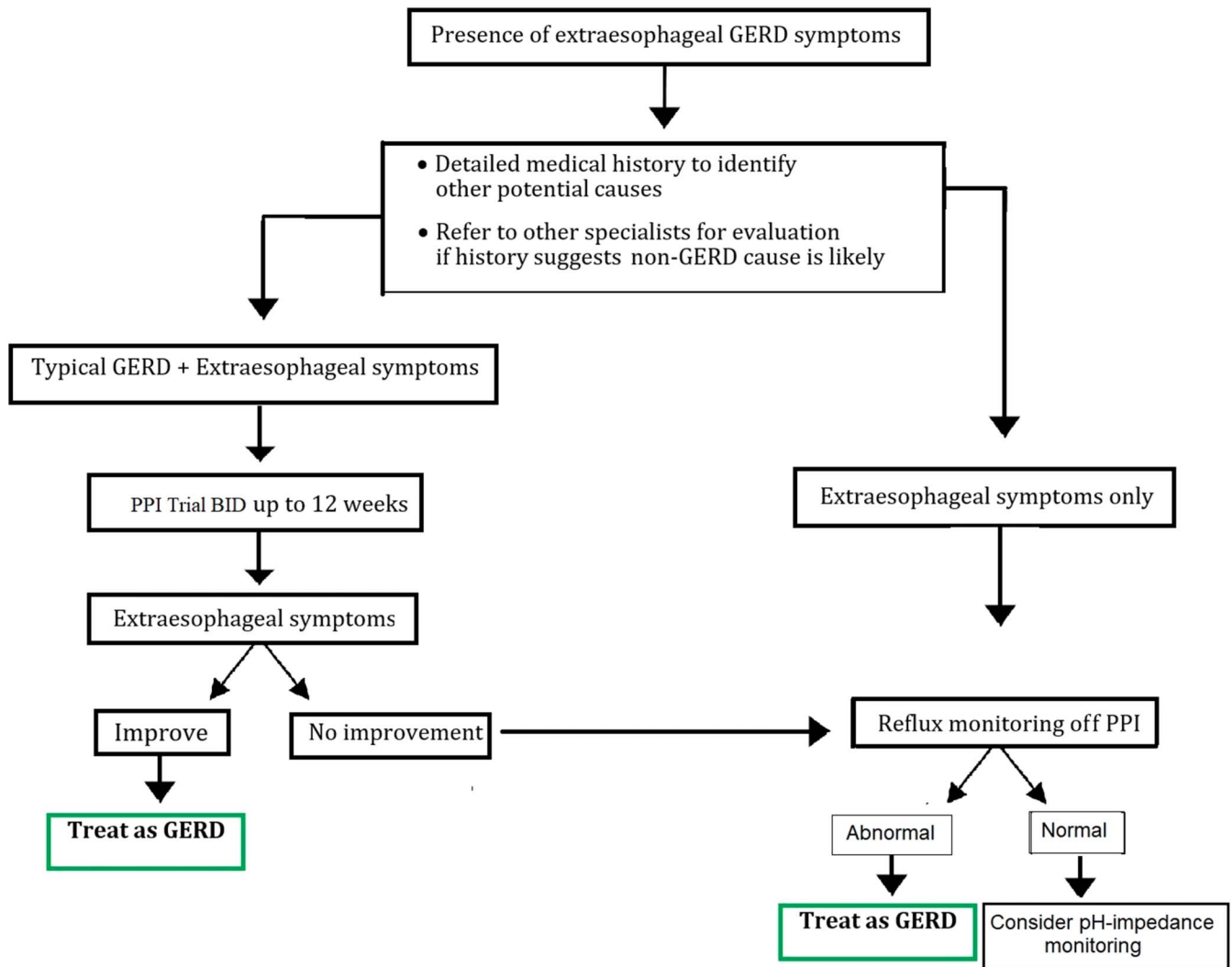
Figure 2. Diagnostic algorithm for extraesophageal GERD symptoms. BID, twice-daily; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

clinical outcomes, 29 different LPR signs and multiple scoring systems were evaluated. LPR signs on laryngoscopy were found to have low specificity, with validation hampered by the lack of a gold standard for diagnosis (90). Inter-rater reliability for laryngeal findings was also found to be low for multiple laryngoscopic features attributed to LPR (91). In 1 study of patients originally believed to have LPR, a careful review of laryngoscopic findings by study investigators identified other causes of the laryngeal complaints including cancer, muscle tension dysphonia, vocal cord paresis, and benign mucosal lesions (92). In 1 recent pediatric study, the laryngoscopic RFS did not correlate with pH-impedance findings, the presence of EE, or quality of life (93). This lack of correlation between laryngoscopic findings and symptoms also been documented in adults. In 1 study of 105 normal, asymptomatic volunteers, 86% had findings associated with reflux on laryngoscopy, with some signs of LPR seen in 70% of participants (94). A second study of normal, asymptomatic volunteers found at least 1 sign of inflammation in 93% of participants who underwent flexible laryngoscopy (95). The use of laryngoscopy for diagnosis of LPR has substantial limitations, with inflammation seen in asymptomatic volunteers, low reproducibility, and lack of correlation between laryngoscopic findings and symptoms. Although ENT physicians often treat LPR based on laryngoscopy findings, a poor response to medical therapy should not be surprising.

Reflux testing
Multichannel pH-impedance testing, traditional catheter-based pH testing, and wireless pH testing have been used to evaluate patients with extraesophageal GERD symptoms. Reflux testing using pH-impedance can detect acidic (pH < 4), weakly acidic (pH 4–7), and nonacidic reflux (pH > 7), and determine the extent of proximal reflux, which may be important in the evaluation of extraesophageal GERD symptoms. pH-impedance testing in patients with LPR symptoms is abnormal in 40% of cases (96). pH-impedance monitoring has been used in several studies of patients with LPR symptoms, and those with abnormal pH-impedance results were found to be more likely to respond to PPI treatment than patients with normal testing (97,98). Studies in which pH-impedance monitoring was used to identify the relationship between reflux events and cough episodes have shown that chronic cough can be associated with weakly acidic and nonacidic reflux events (99,100). In a study of 21 patients with globus and 12 with heartburn alone who were evaluated by pH-impedance testing performed on PPI therapy, proximal

reflux was noted to be more common in the patients with globus (101). Use of pH-impedance in this study increased the yield of standard pH testing by 28% and identified proximal esophageal reflux as a significant predictor of globus.

Presently, the clinical significance of proximal reflux is unclear, and studies have varied in their criteria for defining this entity (102). One study found that extraesophageal symptoms were not more frequently associated with proximal esophageal reflux than typical GERD symptoms and that, irrespective of symptoms, half of all reflux events extended to the proximal esophagus (103). In a study of 237 patients with extraesophageal symptoms refractory to medical therapy, traditional reflux parameters were better predictors of fundoplication outcome than impedance testing, with the presence of heartburn and acid exposure times >12% increasing the probability of surgical success (104). In a retrospective study of 33 patients with refractory reflux symptoms (typical and atypical) evaluated by pH-impedance monitoring on PPIs, only a positive SAP for heartburn or regurgitation was associated with improvement after surgery (105). In the absence of a clear definition of "normal" proximal esophageal reflux, interpretation of impedance results for extraesophageal GERD is problematic, and surgical outcomes seem to be predicted better by traditional reflux parameters.

The choice to test on or off PPIs in patients with extraesophageal symptoms has no clear answer. Testing off PPIs can be used to determine whether pathologic esophageal acid exposure is present and should be considered when the pretest probability for GERD is low. Testing on PPIs can be considered in patients already known to have pathologic acid exposure, such as those with Barrett's esophagus or with LA grade C or D EE (106). One proposed model for determining which patients should undergo pH testing on or off a PPI was developed using a population of 471 patients with refractory heartburn or extraesophageal GERD (107). Risk factors for abnormal esophageal acid exposure in patients with suspected extraesophageal reflux included BMI > 25, hiatal hernia, and presence of heartburn. In patients with extraesophageal symptoms persistent after 2 months of b.i.d. PPIs, the investigators suggest calculation of the Heartburn, Asthma, and BMI Extraesophageal Reflux score—1 point each for BMI > 25, asthma, and heartburn, but no points for cough or hoarseness. pH-impedance testing on PPIs was recommended for patients with a Heartburn, Asthma, and BMI Extraesophageal Reflux score of 3, whereas testing off PPIs was recommended for those with scores ≤2. Other studies attempting to address the question of testing on or off PPIs have found that the total number of reflux episodes detected by impedance is similar between testing on and off PPIs (108,109), whereas 1 study found that patients were more likely to have a positive SAP off PPI (108).

Wireless pH testing also has been used for evaluation of patients with extraesophageal symptoms. In 1 series of patients with extraesophageal GERD symptoms who had wireless pH testing, 81% had abnormal acid exposure, typically mild to moderate reflux, and more often in the upright position (110). However, because wireless pH testing focuses on distal acid reflux only, it is not a reliable index for laryngeal acid exposure. However, if normal over 96 hours of testing, it provides evidence against acid reflux as a cause of symptoms.

Pharyngeal and oropharyngeal reflux monitoring
Catheter-based pharyngeal pH monitoring with dual sensor probes and oropharyngeal pH monitoring have been proposed as methods to better detect LPR compared with traditional pH monitoring and

pH-impedance. However, the reliability of pharyngeal pH measurement has been questioned, and proximal sensor data may be unreliable because of placement issues (111–114). Similar to pH-impedance testing, the amount of proximal reflux considered abnormal varies by study (115–118). A systematic review found no significant differences in dual-channel pH testing results between normal controls and patients with laryngeal symptoms (119).

Early studies of oropharyngeal pH testing were promising and seemed to predict success of antireflux surgery (120,121). However, subsequent studies have failed to identify a significant correlation between oropharyngeal reflux events and pH-impedance reflux events, suggesting that decreases in oropharyngeal pH may be due to factors other than gastroesophageal reflux (122–126). One study of adults with laryngeal symptoms evaluated patients using the reflux SI, video laryngoscopy, and oropharyngeal pH monitoring, followed by a PPI trial (127). There were no significant differences in oropharyngeal acid exposure between PPI responders, partial responders, and nonresponders. Lack of correlation between oropharyngeal pH events and pH-impedance events was seen in another study of adults with suspected LPR—oropharyngeal pH test results were unable to distinguish asymptomatic volunteers from patients with laryngeal irritation (128).

Salivary pepsin testing
Salivary pepsin testing has been proposed as a noninvasive method of detecting LPR. A recent meta-analysis of 11 observational studies examined the role of salivary pepsin testing in diagnosing LPR (129). Significant heterogeneity was found, with varying reference standards for LPR diagnosis (pH monitoring, symptoms, and laryngoscopic signs), different pepsin assays, variable definitions of abnormal tests, and number of pepsin tests performed. Another study found pooled sensitivity of pepsin testing for LPR was 64% and specificity was 68%, with an area under the curve of 0.71 (130). Another meta-analysis of pepsin as a marker of LPR reached similar conclusions and noted that control patients often had elevated salivary pepsin levels (131). Salivary pepsin levels also may vary by time of day, with higher levels in the morning, which limits interpretation (132). A study of children with GERD found no correlation between multichannel pH-impedance and salivary pepsin testing results (130). In a study of adults with laryngeal complaints, pepsin was found in the saliva of 78% of those with laryngoscopic signs of laryngeal inflammation, but in 47% of patients with normal laryngoscopy (131). In another study, pepsin testing was unable to distinguish between healthy adult volunteers and patients with extraesophageal reflux symptoms (133).

PPIs and extraesophageal symptoms
A clinical response to PPI therapy has been proposed as a method to both diagnose and treat extraesophageal GERD (134–136), and has been evaluated in numerous observational studies and RCTs, with 4 meta-analyses and 1 systematic review compiling the results. The efficacy of PPIs in LPR remains unclear because 2 meta-analyses found no significant benefit of PPIs (137,138), whereas 2 found some benefit (139,140). In 1 recent meta-analysis of 10 RCTs of PPI treatment for LPR, the pooled RR of improvement with any PPI treatment was 1.31, with a stronger PPI effect seen in studies that excluded dietary management of LPR (RR 1.42) (139). Another meta-analysis found improved symptoms in LPR patients treated with PPIs compared with placebo, with improvements in SI, but not in the laryngoscopy RFS (140). These analyses showed that the

diagnostic criteria for LPR varied substantially between studies, as did clinical outcomes, treatment regimens, and treatment duration, making recommendations for use of PPIs in LPR challenging (139,141).

Although PPI treatment is often the first step in the management of LPR, this approach may need to be reconsidered. One study comparing up-front reflux testing for LPR patients rather than starting them on empiric PPI therapy found that overall evaluation and treatment costs were lower with initial pH-impedance and esophageal manometry testing (142). Also, a comparison of several algorithms for managing LPR revealed that total costs of therapy were lower in LPR patients treated with initial twice-daily PPI dosing rather than once-daily PPI dosing (142).

Recent studies have questioned the role of PPI therapy for patients with asthma. Two RCTs, 1 in adults and 1 in children, showed no benefit in controlling asthma symptoms in patients on twice-daily PPIs (84,85). One systematic review on the role of PPIs in asthma found a small improvement in morning peak expiratory flow that was unlikely to be clinically meaningful (143). One RCT did show improved asthma symptoms in patients on twice-daily PPIs, but only in patients with GERD with nocturnal respiratory symptoms (144). Chronic cough has also been attributed to GERD, but recent studies and systematic reviews suggest that PPIs are not effective in treating chronic cough in most patients (82,145–147).

Surgery

Antireflux surgery has been used to treat patients with extraesophageal GERD symptoms, but outcomes are inferior to those of antireflux surgery for patients with traditional GERD symptoms. Two systematic reviews (involving primarily studies that were small, retrospective, and uncontrolled) have examined the relationship among extraesophageal GERD symptoms, esophageal acid exposure, and surgical outcomes (148,149). The range of reported improvement in extraesophageal symptoms was wide, ranging from 15% to 95%, with extraesophageal symptoms having poorer response to surgical treatment than typical GERD symptoms.

In 1 study, patients for whom PPIs provided only incomplete relief of laryngeal symptoms despite normalizing esophageal acid exposure were offered antireflux surgery. At 1 year, only 10% of patients who underwent surgery and 7% of patients who continued medical therapy for GERD had improvement in laryngeal symptoms. However, two-thirds of patients who pursued nonsurgical, non-GERD treatments for laryngeal symptoms had improved symptoms at 1 year (150). This study illustrates the importance of pursuing non-GERD treatments for unexplained laryngeal symptoms. Several observational studies and 1 RCT have suggested that antireflux surgery can improve asthma symptoms. In the 1 RCT, 74% of surgically treated patients (n = 16) had improvement in asthma symptoms compared with 9% on H2RAs and 4.2% in the control group (151). Observational studies of antireflux surgery for patients with asthma suggest that asthma symptoms can improve, but improvement in pulmonary function tests and objective parameters is inconsistent (151–153). Furthermore, heterogeneity in inclusion criteria and surgical techniques among studies make it difficult to draw meaningful conclusions about the efficacy of antireflux surgery for treating asthma.

Predicting which patients with extraesophageal symptoms will improve with antireflux surgery is challenging. In 1 study of patients with extraesophageal symptoms, predictors of symptomatic improvement after surgery included the presence of heartburn with or without regurgitation and abnormal acid exposure time on pH testing (104). Recurrence of extraesophageal symptoms after surgical therapy is also a concern. One retrospective cohort study compared adults with extraesophageal GERD (n = 36) and typical reflux symptoms (n = 79), all of whom had abnormal distal esophageal acid exposure. Recurrence of symptoms after surgery was more likely in patients with extraesophageal symptoms and in those who had a poor response to preoperative PPI therapy (154). Patients with extraesophageal symptoms that do not respond to PPIs and patients without objective evidence of reflux should avoid surgical or endoscopic treatment of GERD.

REFRACTORY GERD

The below recommendations for the management of refractory GERD are also illustrated in Figure 3A and 3B.

Recommendations

1. We recommend optimization of PPI therapy as the first step in management of refractory GERD (strong recommendation, moderate level of evidence).
2. We suggest esophageal pH monitoring (Bravo, catheter-based, or combined impedance-pH monitoring) performed OFF PPIs if the diagnosis of GERD has not been established by a previous pH monitoring study or an endoscopy showing long-segment Barrett's esophagus or severe reflux esophagitis (LA grade C or D) (conditional recommendation, low level of evidence).
3. We suggest esophageal impedance-pH monitoring performed ON PPIs for patients with an established diagnosis of GERD whose symptoms have not responded adequately to twice-daily PPI therapy (conditional recommendation, low level of evidence).
4. For patients who have regurgitation as their primary PPI-refractory symptom and who have had abnormal gastroesophageal reflux documented by objective testing, we suggest consideration of antireflux surgery or TIF (conditional recommendation, low level of evidence).

Key concepts

1. It is important to stop PPI therapy in patients whose off-therapy reflux testing is negative, unless another indication for continuing PPIs is present.
2. Esophageal manometry should be considered as part of the evaluation for refractory GERD in patients with a normal endoscopy and pH monitoring study and for patients being considered for surgical or endoscopic treatment.
3. If not already performed off PPIs, we recommend diagnostic upper endoscopy after discontinuing PPI therapy, ideally for 2 to 4 weeks. Esophageal biopsies should be performed even if endoscopy reveals normal mucosa.
4. We recommend performing high-resolution esophageal manometry in patients with refractory GERD if reflux monitoring and endoscopy are unrevealing.

It has been suggested that up to 40% of patients treated with PPIs will report persistent symptoms of heartburn and regurgitation, with negative effects on quality of life (155–157). One systematic review of GERD studies found that persistent GERD
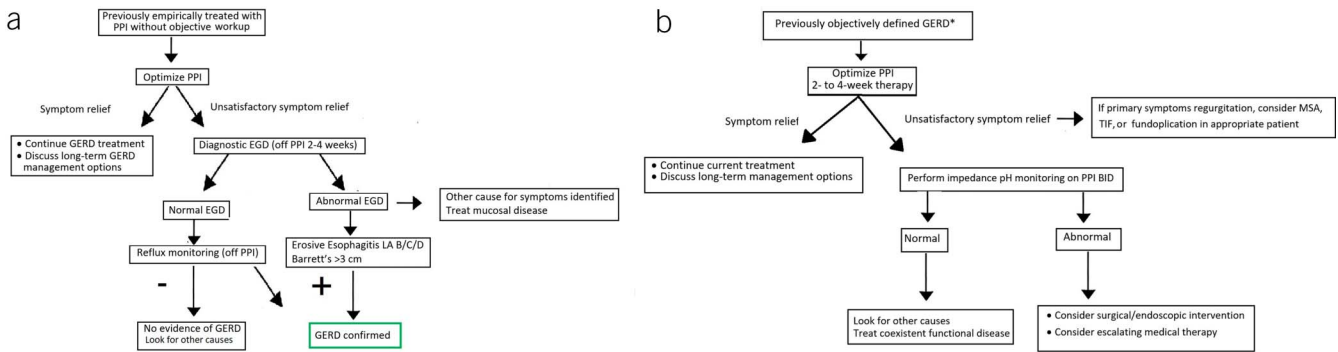
Figure 3. (**a**) Management algorithm of symptoms suspected because of GERD incompletely responsive to PPIs, previously empirically treated with PPI without objective workup. GERD, gastroesophageal reflux disease; EGD, esophagogastroduodenoscopy; LA, Los Angeles; PPI, proton pump inhibitor. (**b**) Management algorithm of symptoms suspected because of GERD incompletely responsive to PPIs in patients previously objectively defined as GERD. *LA B/C/D GERD, gastroesophageal reflux disease; EGD, esophagogastroduodenoscopy; LA, Los Angeles; MSA, magnetic sphincter augmentation; PPI, proton pump inhibitor; TIF, transoral incisionless fundoplication.

symptoms were present in 32% of patients participating in primary care–based randomized trials of GERD therapy, with 45% of patients in observational studies having persistent symptoms (156). Although there are limited data evaluating the benefit of twice-daily PPIs for patients with GERD symptoms refractory to once-daily PPIs (158), GERD generally has not been considered "PPI-refractory" unless the patient has been on PPIs b.i.d. The most commonly accepted definition of refractory GERD is persistent heartburn and/or regurgitation despite 8 weeks of double-dose PPI therapy (159). Other authorities consider persistent symptoms after 12 weeks on double-dose PPIs to be refractory GERD (160). These patient-driven definitions, while pragmatic, are broad.

Similarly, the terms "complete relief/response," "partial relief/response," and "no response" have been arbitrarily and poorly defined, and duration of symptoms and PPI dosing vary across studies (156,161). GERD is a disease with multiple symptom presentations that respond variably to PPIs. Heartburn is more likely to respond to PPIs than regurgitation or extraesophageal symptoms. As such, it is clinically useful to separate refractory heartburn, regurgitation, and extraesophageal symptoms when thinking about these patients. Table 4 lists 4 potential mechanisms of refractory GERD.

There are 2 broad groups of patients with symptoms despite PPI therapy. One group is patients with symptoms suspected to be GERD-related who have been empirically treated with a PPI (typically once-daily then increased to twice-daily) yet remain symptomatic. The second group of patients has objective evidence of GERD, with endoscopic findings of EE or Barrett's esophagus and/or reflux testing showing abnormal esophageal acid exposure, who have incomplete or no response to PPIs. When discussing the overall approach to patients with GERD symptoms not relieved by PPIs, it is prudent to discuss management of these 2 groups separately.

History and physical examination

The evaluation of refractory GERD should begin with a careful history and physical examination. This will enable the clinician to make a meaningful assessment of the likelihood that GERD is causing the bothersome symptoms and may provide clues to the presence of nonesophageal disorders. If no obvious nonesophageal disorders are present, then optimization of PPI therapy is recommended. This is critical for managing patients with persistent GERD symptoms, regardless of whether the patient has been empirically treated or carries an objective diagnosis of GERD.

Optimization of PPI therapy

Optimization of PPI therapy includes verifying compliance, confirming that the PPI is taken 30–60 minutes before the first meal of the day for daily dosing and before the first and dinner meal for twice-daily dosing (162). A study analyzing data from randomized trials in which gastric pH monitoring was performed in patients receiving various PPI formulations concluded that twice-daily PPI therapy is superior to once-daily double-dose PPI therapy in maintaining gastric pH above 4 during a 24-hour monitoring period (53). We analyzed data from randomized clinical trials that performed pH testing in patients receiving single-dose PPI formulations. In 1 study, patients with good symptom control took daily PPIs on 84% of days, compared with patients with poor symptom control, who took PPIs on only 55% of days (163), with similar findings seen in other studies (81). In a recent randomized, multicenter trial of Veterans with heartburn refractory to PPI treatment, 42 of 366 (11.4%) participants had ≥50% improvement in GERD symptoms when omeprazole use was optimized, with dosing 30 minutes before breakfast and dinner (24). Another study of patients with NERD with typical GERD symptoms despite PPI use found that 35% responded to daily esomeprazole when dosed correctly (164). A smaller trial examined the effects of optimizing daily omeprazole compared with *ad lib* dosing and found improvement in symptoms and GERD quality-of-life scores in those receiving education on proper dosing of daily PPIs (165). Some studies have found that doubling the PPI dose or dosing twice daily can help with persistent typical symptoms of GERD, as can switching to a different PPI (59,166). Regardless of dose, a small, but clinically significant number of patients will have symptom improvement with the simple, low-cost intervention of optimizing PPI therapy.

Endoscopy

Endoscopy is the next step to investigate persistent GERD symptoms and evaluate alternative diagnoses. Performing endoscopy after a PPI holiday might increase the yield for identifying EE or determine whether an alternative diagnosis, such as EoE, is responsible for symptoms. A recent study found that EE can relapse within 2 weeks after stopping PPIs, with some patients

Table 4. Potential mechanisms underlying symptoms suspected due to GERD but refractory to PPI therapy

Despite PPI therapy, abnormal acid reflux persists and is causing symptoms
There is reflux hypersensitivity, a condition in which PPIs have normalized esophageal acid exposure, but "physiologic" reflux episodes (acidic or nonacidic) nevertheless are strongly associated with and evoke symptoms
The symptoms are not due to GERD, but are caused by esophageal disorders other than GERD (e.g., EoE and achalasia)
The symptoms are not due to GERD, but are caused by nonesophageal disorders (e.g., gastroparesis, rumination, and heart disease)
The symptoms are functional (i.e., not because of GERD or any other identifiable histopathologic, motility, or structural abnormality).

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

even developing LA grade C EE (63). EoE has been seen in 1%–8% of patients with refractory GERD (24,167–170). Temporarily discontinuing PPIs before endoscopy in these patients may unmask the EoE histology, which could be obscured if endoscopy is performed on PPIs, missing an opportunity to identify the cause of ongoing GERD symptoms. In patients with persistent GERD symptoms on PPIs, there is a low likelihood of finding reflux esophagitis if PPIs are not stopped before endoscopy (17,171).

Reflux monitoring

Regardless of symptom presentation, it is imperative to document the presence of abnormal or ongoing reflux to plan treatment options for patients with persistent GERD symptoms. Reflux monitoring can identify patients with ongoing acid reflux, weakly acidic, nonacidic reflux, adequate acid control but ongoing symptoms, and normal reflux parameters. Depending on the clinical situation, performing monitoring off PPIs for 7 days or testing for acid, weakly acidic, and nonacid reflux while on PPIs can be considered.

The choice of test and whether to test on or off PPIs is dependent on the question being asked. If the patient has been empirically treated (never had an objective diagnosis of GERD), or the clinician believes the likelihood that reflux is the cause of symptoms is low, or for patients considering surgery, an off-therapy study should be considered (17,159). A recent study investigated the utility of 96-hour capsule-based pH monitoring off PPI therapy in patients with persistent typical symptoms despite PPI treatment to determine whether PPIs could be stopped. Patients with 2 or more days with esophageal acid exposure time >4 percent were unlikely to be able to stop PPIs. Those with a normal study on all 4 days were the group with the highest likelihood of being able to discontinue PPIs (172).

On-therapy monitoring is suggested before surgery or endoscopic intervention in patients with previous objective findings of GERD (such as Barrett's esophagus or LA grade C/D EE) who have continued symptoms despite PPI treatment (17). Although retrospective studies suggest that patients with GERD symptoms unresponsive to PPIs who are proven to have GERD by off-therapy pH monitoring can respond to surgery (108), and some interventionalists endorse antireflux procedures based on off-therapy pH monitoring for such patients (173), the documentation of persistent abnormal acid reflux on PPIs or of a positive association between symptoms and reflux episodes offers "reassurance" that surgery or endoscopic therapy can be successful in the PPI-refractory patient.

Several studies have attempted to address the question of testing on or off PPIs in patients with persistent GERD. The total number of reflux episodes detected by impedance is similar between testing on and off PPIs (108,174,175). Other studies have used reflux testing to guide therapy for patients with refractory GERD symptoms.

Reflux testing combined with other testing, such as esophageal manometry, gastric emptying studies, and endoscopy, identified a diagnosis of GERD in only 34.5% of cases in 1 study (176). In a multicenter study, only 21% of patients with persistent heartburn on PPIs were found to have truly refractory GERD (24). Overall, the balance of data suggests that few patients with refractory GERD symptoms on PPIs have continued reflux as the cause for symptoms, suggesting value for a tailored approach using impedance-pH monitoring before intervention (24). For on-therapy reflux monitoring, we recommend that PPIs be taken twice-daily, the approach used in the randomized trial of medical vs surgical therapy for PPI-refractory reflux disease (24). Furthermore, impedance-pH monitoring rather than pH monitoring alone is recommended for on-therapy reflux monitoring, both because the yield of pH monitoring in this setting is so low (fewer than 10% of patients on twice-daily PPIs have persistently abnormal acid reflux (160)) and because impedance monitoring enables correlation between symptoms and nonacid reflux episodes. It is important to stop PPI therapy in patients whose off-therapy reflux testing is negative, unless a previous diagnosis of GERD had been made or another indication for continuing PPIs is present. In 1 study, 42% of patients reported continuing PPI treatment after a negative evaluation for refractory GERD, which included negative endoscopy and pH-impedance monitoring (2).

Esophageal manometry

Some patients with motility disorders such as achalasia or esophageal spasm will report heartburn symptoms. In studies of patients with refractory GERD, 1%–3% of patients are found to have achalasia when manometry is performed (24,177). Patients with esophageal aperistalsis are identified in roughly 3% of manometry tests performed for evaluation of GERD (177). These patients often report heartburn symptoms and have a poor response to antireflux surgery. Other disorders, such as rumination and supragastric belching, may also detected by esophageal manometry.

Surgery

Recent publications have changed the thought process on surgical intervention for some patients with refractory GERD. Randomized trials compared MSA with continued medical therapy in patients with regurgitation refractory to PPIs. MSA improved symptoms more than continued medical therapy in patients with objective documentation of abnormal reflux (178,179). Two randomized trials with TIF also demonstrate better improvement in

regurgitation with TIF compared with high-dose PPIs, although the magnitude of improvement was not as great as with MSA (180). A recent study illustrates the challenge of managing refractory GERD. In this study of medical vs surgical treatment for 366 patients with heartburn that failed to respond to PPIs, extensive evaluation revealed that heartburn symptoms were truly PPI-refractory and reflux-related in only 78 patients (21%) (24).

Identifying patients with true refractory GERD is crucial because surgery (or endoscopic treatment) may truly be best in this group. For patients with regurgitation refractory to PPI therapy, care should be taken to distinguish regurgitation from rumination, a functional disorder characterized by effortless food regurgitation during or soon after eating, typically with rechewing, reswallowing, or spitting out of the regurgitated material. Surgical treatment is not recommended for patients with rumination (181). A detailed discussion of the management of functional heartburn and other functional upper GI symptoms exceeds the scope of this guideline.

SURGICAL AND ENDOSCOPIC OPTIONS FOR GERD

Recommendations

1. We recommend antireflux surgery performed by an experienced surgeon as an option for long-term treatment of patients with objective evidence of GERD, especially those who have severe reflux esophagitis (LA grade C or D), large hiatal hernias, and/or persistent, troublesome GERD symptoms (strong recommendation, moderate level of evidence).
2. We recommend consideration of MSA as an alternative to laparoscopic fundoplication for patients with regurgitation who fail medical management (strong recommendation, moderate level of evidence).
3. We suggest consideration of Roux-en-Y gastric bypass (RYGB) as an option to treat GERD in obese patients who are candidates for this procedure and who are willing to accept its risks and requirements for lifestyle alterations (conditional recommendation, low level of evidence).
4. Because data on the efficacy of radiofrequency energy (Stretta) as an antireflux procedure is inconsistent and highly variable, we cannot recommend its use as an alternative to medical or surgical antireflux therapies (conditional recommendation, low level of evidence).
5. We suggest consideration of TIF for patients with troublesome regurgitation or heartburn who do not wish to undergo antireflux surgery and who do not have severe reflux esophagitis (LA grade C or D) or hiatal hernias >2 cm (conditional recommendation, low level of evidence).

Key concepts

1. We recommend HRM before antireflux surgery or endoscopic therapy to rule out achalasia and absent contractility. For patients with ineffective esophageal motility, HRM should include provocative testing to identify contractile reserve (e.g., multiple rapid swallows).
2. Before performing invasive therapy for GERD, a careful evaluation is required to ensure that GERD is present and as best as possible determine is the cause of the symptoms to be addressed by the therapy, to exclude achalasia (which can be associated with symptoms such as heartburn and regurgitation that can be confused with GERD), and to exclude conditions that might be contraindications to invasive treatment such as absent contractility.

In most patients, the symptoms and endoscopic signs of GERD resolve readily with medical treatment, and invasive antireflux therapies are neither required nor desired by patients. However, GERD is a chronic disease, and patients often require protracted medical treatment, which is inconvenient and carries some risk. Severe reflux esophagitis (LA grade C and D) does not heal reliably with any medical therapy other than PPIs, and studies have demonstrated that severe EE returns quickly in most patients when PPIs are stopped (18,182,183). It might be possible to reduce or even eliminate medical therapy for patients with mild forms of GERD (e.g., no reflux esophagitis worse than LA grade B), but patients with severe reflux esophagitis (LA grade C or D) will require PPI therapy indefinitely to maintain healing. In light of recent concerns regarding the safety of long-term PPI usage, many patients are uncomfortable with the prospect of lifelong PPI treatment. Although antireflux procedures have their own well-established risks, some of which are serious, there are a number of patients who prefer to opt for those over the putative risks and inconvenience of lifelong PPI therapy.

GERD that fails to respond to medical therapy is another valid indication for antireflux procedures, but one that requires meticulous preprocedure evaluation to achieve good surgical outcomes. Before the advent of PPIs, failure to respond to medical therapy was the major indication for antireflux surgery. Today, however, PPI therapy is so effective for treating typical GERD symptoms such as heartburn and regurgitation that failure to respond to PPIs should be regarded as a red flag that GERD may not be the underlying cause. Indeed, patients who have the best response to antireflux surgery are those with typical GERD symptoms who respond well to PPIs (184,185), presumably because these patients clearly have abnormal gastroesophageal reflux, and antireflux surgery is highly effective at controlling that problem. Although it is claimed that 30%–40% of patients treated with PPIs for GERD have persistent "GERD symptoms" (186,187), in many cases, those PPI-resistant symptoms are mistakenly assumed to be caused by reflux. Symptoms that are not reflux-related will not respond to antireflux procedures; yet, these procedures often have been used (and failed) in patients who had little or no objective evidence of underlying GERD. It is critical to establish that "refractory GERD symptoms" are indeed reflux-related before recommending invasive antireflux treatment.

In a recent study of medical vs surgical treatment for PPI-refractory heartburn that included 366 patients referred to GI clinics because of heartburn that failed to respond to PPIs, extensive workup revealed that the heartburn was truly PPI-refractory and reflux-related in only 78 patients (21%) (24). Among the other 288 patients, heartburn was relieved in 42 (12%) when they were given a trial of twice-daily omeprazole with explicit instructions on how to take the medication properly, 70 (19%) were unwilling or unable to complete the rigorous preoperative workup required for trial entry, 54 (15%) were excluded for miscellaneous reasons, 23 (6%) had non-GERD esophageal disorders such as EoE and achalasia, and 99 (27%) had functional heartburn. For the 78 patients in whom rigorous workup established that the PPI-refractory heartburn was indeed reflux-related, treatment success (≥50% improvement in GERD Health-Related Quality-of-Life symptom scores at 1 year) for laparoscopic Nissen fundoplication (18/27, 66.7%) was significantly superior to active medical (7/25, 28.0%, $P = 0.007$) and placebo medical (3/26, 11.5%, $P < 0.001$) treatments.

Although heartburn is the cardinal symptom of GERD, the aforementioned study shows that PPI-refractory heartburn is uncommonly due to GERD. As discussed above establishing a clear causal relationship with GERD can be even more difficult for so-called "extraesophageal GERD symptoms" such as throat clearing, hoarseness, and chronic cough. Surgical treatment of extraesophageal GERD is reviewed in detail in the "extraesophageal GERD section." Few high-quality data have established the benefit of invasive treatments for patients with these extraesophageal GERD symptoms, and physicians should be extra cautious in recommending such treatments for patients with LPR and other "extraesophageal GERD symptoms." Only persistent abnormal acid reflux and reflux hypersensitivity are likely to benefit from antireflux procedures.

Fundoplication

Fundoplication, especially Nissen fundoplication, is widely regarded as the "gold standard" among the antireflux procedures for its efficacy in improving the physiologic parameters of GERD such as LES pressure and esophageal acid exposure time (188). Fundoplication creates a barrier to the reflux of all gastric material (acidic and nonacidic) and therefore should be an effective treatment for any GERD symptom that is reflux-related.

Interest in surgical antireflux therapy intensified in the 1980s when observational studies described >90% efficacy for fundoplication in controlling GERD symptoms over a 10-year period (189). Interest in fundoplication was further fueled by a randomized trial conducted by the Veterans Administration in the late 1980s (when antireflux surgery was performed as an open procedure and before PPIs were available) which found that open Nissen fundoplication was significantly more effective than ranitidine-based medical therapy in healing the symptoms and endoscopic signs of complicated GERD for the 2-year duration of the study (190). However, a long-term follow-up investigation published in 2001 showed that after 10–13 years, 23 (62%) of 37 surgical patients for whom follow-up was available reported that they were once again taking antireflux medications on a regular basis to treat their GERD symptoms, and surgically treated patients had decreased long-term survival largely because of excess deaths from heart disease (191). This report and other developments resulted in a long decline in the use of operative treatment for GERD.

Laparoscopic antireflux surgery (LARS) was introduced in 1991, and this has since become the standard operative approach to fundoplication, essentially replacing open antireflux surgery. Studies focusing on the durability of modern surgical technique have found a wide range of GERD recurrence rates. Cohort studies often found high rates of postoperative antireflux medication usage (up to 43%) (192–196), whereas several randomized trials of LARS vs medical therapy conducted at specialized centers described lower GERD recurrence rates (10%–27% during follow-up periods of 3–5 years) (197–199).

A recent systematic review and meta-analysis focusing on patient-relevant outcomes of fundoplication vs PPI-based medical management of GERD found that heartburn and regurgitation were less frequent with surgical than with medical therapy and, although a considerable proportion of patients still needed antireflux medications after fundoplication, surgical patients were significantly more satisfied with their treatment in the short and medium term (200). However, a more recent Cochrane review concluded that there is considerable uncertainty in the balance of benefits vs harms of laparoscopic fundoplication compared with long-term PPI therapy and called for further randomized, controlled trials (201). Compared with Nissen (complete) fundoplication, partial fundoplications (e.g., Toupet and Dor) seem to have similar efficacy in relieving GERD symptoms, but result in less postoperative dysphagia, gas-bloat, and inability to belch and vomit (202–205). However, partial fundoplication also might have a higher rate of recurrent GERD (205).

A recent report of a retrospective, population-based cohort study has shed considerable light on the outcome of LARS performed in a "real-world" setting (206). The study involved 2,655 patients identified in the Swedish Patient Registry as having had primary LARS performed between 2005 and 2014. During a mean follow-up period of 5.1 years, 470 patients (17.7%) had a reflux recurrence (i.e., 393 used PPIs/H2RAs for >6 months, and 77 had repeat antireflux surgery). Within 30 days of surgery, 109 patients (4.1%) had complications such as infection, bleeding, and esophageal perforation, and there were only 2 deaths (0.1%), neither of which was directly related to the operation. Postoperative dysphagia was documented in 21 patients (0.8%), including 14 (0.5%) who required endoscopic dilatation. This report suggests that LARS can be performed with a relatively low rate of morbidity, and with a very low mortality rate, considerably lower than that of the old open antireflux surgery. The study did not assess patient-reported outcomes or the use of over-the-counter medications, and it is well known that LARS occasionally can have catastrophic short- and long-term complications. Nevertheless, it seems to be well tolerated in most cases, and the observation that >80% of patients did not resume the use of antireflux medications suggests that the operation provides long-lasting relief of GERD symptoms for most patients. How patients and physicians view the 17.7% recurrence rate is a matter of personal perspective.

In summary, modern medical antireflux therapy and laparoscopic fundoplication seem to have similar efficacy in healing the symptoms and endoscopic signs of GERD. Recent concerns about the safety of long-term PPI therapy and refinements in surgical technique that have substantially decreased its morbidity and mortality have rekindled interest in fundoplication. Clearly, antireflux surgery is not a permanent cure for GERD in all patients as it was once touted to be, and the operation occasionally can have severe adverse effects. Nevertheless, most patients obtain long-term benefit from fundoplication, and patient satisfaction with successful surgery seems to be greater than that for chronic medical therapy. The major question for patients considering antireflux surgery is this: Does the >80% possibility of long-term freedom from PPIs and their attendant risks warrant the 4% risk of acute complications of fundoplication and its 17.7% risk of GERD recurrence? (207).

Magnetic sphincter augmentation

MSA with the LINX Reflux Management System, a necklace of titanium beads with magnetic cores that encircles the distal esophagus to bolster the LES and prevent reflux, was developed as a less invasive and more readily reversible GERD treatment than fundoplication. The initial target population for MSA was patients with GERD with abnormal acid reflux documented by esophageal pH monitoring (off PPIs) who experienced only partial relief with PPIs and who did not have large hiatal hernias or severe reflux esophagitis (208). For 100 such patients in an early pilot study with no control group, 92% achieved ≥50% improvement in quality-of-life scores, 93% reduced their PPI

usage by ≥50%, and 64% had ≥50% reduction in esophageal acid exposure at 1 year (208). Dysphagia was the most frequent adverse event, experienced by 68% of patients in the postoperative period, by 11% at 1 year, and by 4% at 3 years. Six patients had serious adverse events, and 6 eventually had the device removed. In a 5-year follow-up of patients in this study, there were no device erosions or migrations, 85% of patients had discontinued their use of PPIs, and all patients reported the ability to belch and vomit (209).

Although large hiatal hernias and severe reflux esophagitis were contraindications to MSA in early studies of the technique, subsequent studies have found that the short-term clinical outcomes of MSA for patients with those conditions are similar to those described for patients with less severe forms of GERD (210–212). Unlike the minimal surgical dissection required for implantation of the device in patients with small hiatal hernias, however, patients with large hiatal hernias require a more extensive dissection and repair of the crural diaphragm.

One problem with implantation of the metallic MSA device is that patients cannot have magnetic resonance imaging with scanning systems >1.5 T. An early concern regarding MSA was that the device would erode into the esophagus. A recent study of data provided by the manufacturer (Ethicon, Summit, NJ) and the MAUDE database on 9,453 devices placed between 2007 and 2017 found that the risk of erosion was 0.3% at 4 years (213). The median time to erosion was 26 months, and most occurred between 1 and 4 years after device implantation. Most of the eroded devices were removed by a combination of endoscopy and laparoscopy, and there were no serious complications of device removal. Thus, device erosion seems to be infrequent and safely managed.

To date, there has been no publication of a randomized trial directly comparing MSA with the gold-standard surgical treatment of laparoscopic fundoplication. However, observational cohort studies have compared the techniques, and systematic reviews and meta-analyses of those reports have arrived at generally similar conclusions (214–217). Compared with fundoplication, MSA has shorter operative times and shorter durations of hospital stays. There seem to be no significant differences between MSA and fundoplication in rates of GERD symptom control, postoperative PPI usage, major complications including dysphagia, and rates of reoperation. Most, but not all, reports suggest that MSA results in less gas-bloat and greater ability to belch and vomit than fundoplication.

A recent randomized trial has established the unequivocal superiority of MSA over twice-daily PPIs for the control of regurgitation (179). In this study, 152 patients with moderate to severe regurgitation despite once-daily PPI therapy were randomly assigned to receive twice-daily PPIs (n = 102) or MSA (n = 50), and MSA was offered to patients in the twice-daily PPI group who had persistent regurgitation after 6 months of treatment. At 1 year, control of regurgitation was achieved in 72 of 75 patients (96%) in the MSA group, but in only 8 of 43 patients treated with PPIs (19%). MSA was not associated with any perioperative events, device explants, erosions, or migrations.

MSA also seems to have a role in the treatment of GERD that worsens or develops after bariatric operations such as sleeve gastrectomy and RYGB (218). These operations alter gastric anatomy in a way that can preclude performance of a standard fundoplication. Limited data suggest that MSA is safe and effective for treating GERD in this setting.

In summary, MSA seems to be a safe and effective alternative to laparoscopic fundoplication. Clinical outcomes of the 2 procedures are similar, and both have unique advantages and disadvantages. The minimal surgical dissection required for MSA results in greater technical ease, shorter operative times, and shorter durations of hospital stays than for fundoplication. MSA is also easier to reverse, and MSA may result in less gas-bloat and greater ability to belch and vomit than fundoplication. The magnetic resonance imaging restriction after MSA is a disadvantage, and compared with fundoplication, there is a paucity of long-term data on MSA outcomes. With no randomized trials comparing the 2 procedures, it is difficult to recommend one over the other at this time.

Roux-en-Y gastric bypass

GERD is strongly associated with obesity. Compared with individuals with a normal BMI, the prevalence of GERD in those whose BMI exceeds 35 is increased up to 6-fold (219). Obesity poses technical challenges to the performance of fundoplication surgery. In addition, the elevated intra-abdominal pressure associated with obesity might put strain on the diaphragmatic hiatus, resulting in fundoplication disruption and herniation, increased surgical complications, and poor outcomes. RYGB can control GERD in obese patients, presumably because the small gastric pouch fashioned during RYGB produces far less acid than an intact stomach, and because the accompanying long alimentary loop prevents the reflux of bile. Because of the widespread perception among surgeons that fundoplication has poor outcomes in obese patients, and the fact that RYGB has been shown both to control reflux and induce weight loss, RYGB has come to be considered the antireflux surgery of choice for obese patients, in whom it is used both as a primary antireflux procedure and as a means for correction of a failed fundoplication (220,221). However, there is now considerable controversy regarding the role of RYGB as an antireflux procedure.

One reason for the controversy is the substantial variability in results of studies on outcomes and rates of complications for fundoplication in obese patients. Some studies have documented poorer results of fundoplication in the obese (222), whereas others have found no differences in complications and outcomes between obese and nonobese patients (223). A recent systematic review and meta-analysis on this issue found no significant differences between obese and nonobese patients in the rates of perioperative complications, redo surgery, and conversion from laparoscopic to open surgery, but the recurrence of reflux after fundoplication was significantly lower in the nonobese patients (OR 0.28; 95% CI, 0.13–0.61, $P = 0.001$) (224). Other reasons for controversy on the role of RYGB include the lack of randomized trials comparing it directly with fundoplication, and the fact that, although RYGB can have numerous beneficial effects, it is a technically difficult operation that produces major alterations in anatomy, which can result in serious early and late complications (225). In addition, a recent, nationwide cohort study of all adults with preoperative reflux who underwent gastric bypass in Sweden between 2006 and 2015 found that, in 2,454 participants followed for median 4.6 years, reflux recurred in 48.8% (95% CI, 46.8–51.0) within 2 years of the operation (226). The authors concluded that the efficacy of gastric bypass for GERD symptoms might have been overestimated. Finally, reports have documented the occasional new development of GERD after RYGB (218).

With all the above-noted uncertainty, an argument can be made to regard RYGB primarily as a highly effective weight loss operation that has the added potential benefit of controlling acid reflux, rather than as an antireflux operation primarily. Obese patients with GERD should be adequately counseled and willing to accept the risks and lifestyle demands of bariatric surgery before undergoing RYGB for control of GERD.

Endoscopic antireflux therapies

A number of endoscopic devices for treating GERD have been introduced over the past 2 decades, and most have been withdrawn from the marketplace because of concerns regarding safety and efficacy. Presently, the only endoscopic GERD treatments still widely available are radiofrequency antireflux treatment (Stretta; Restech, Houston, TX) and TIF (endogastric solutions). Studies of the endoscopic procedures generally have excluded patients with hiatal hernias >2 cm, grade C and D EE, esophageal strictures, and long-segment Barrett's esophagus. Consequently, if these devices are to be used at all, based on data, their use should be limited to patients with milder forms of GERD.

The Stretta procedure is difficult to evaluate, in part because it is not totally clear how it functions as an antireflux therapy. Initially, it was believed to control reflux by inducing swelling and mechanical alteration at the esophagogastric junction. However, an early, sham-controlled trial found that, 6 months after treatment, Stretta had significantly improved GERD symptoms and quality of life, but it did not decrease esophageal acid exposure (227). This raised the possibility that the procedure might alleviate GERD symptoms by altering sensation in the distal esophagus. Systematic reviews and meta-analyses have arrived at contradictory conclusions regarding Stretta's efficacy. One meta-analysis that evaluated only RCTs found that Stretta did not produce significant changes in esophageal acid exposure, quality of life, or the ability to stop PPIs (228), whereas another meta-analysis that included both controlled and cohort studies concluded that Stretta significantly reduced esophageal acid exposure, improved quality of life, and decreased PPI usage (229). Nevertheless, in 2013, the Society of American Gastrointestinal and Endoscopic Surgeons gave Stretta a strong recommendation for use in patients who refuse laparoscopic Nissen fundoplication (230).

TIF attempts to create a flap valve involving 180° to 270° of the circumference of the esophagogastric junction by plicating a portion of the proximal stomach using a series of T-fasteners. Randomized trials have shown that TIF is effective for treating troublesome regurgitation (180,231), but the long-term benefit of TIF is not established and questionable (217). One recent systematic review and meta-analysis on the use of TIF for refractory GERD found that TIF resulted in significant improvements in GERD health-related quality of life and DeMeester scores, enabling 89% of patients to discontinue PPIs (232). However, another systematic review and meta-analysis on the use of TIF for the treatment of GERD found that although symptoms responded to TIF significantly more often that to PPIs/sham, TIF did not result in significant improvement in esophageal acid exposure and most patients resumed PPIs at reduced dosages during long-term follow-up. The incidence of serious adverse events (perforation and bleeding) was 2.4%, and the rate of total satisfaction with TIF was 69% by 6 months (233).

LONG-TERM PPI ISSUES
Key concepts

1. Regarding the safety of long-term PPI usage for GERD, we suggest that patients should be advised as follows: "PPIs are the most effective medical treatment for GERD. Some medical studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. Those studies have flaws, are not considered definitive, and do not establish a cause-and-effect relationship between PPIs and the adverse conditions. High-quality studies have found that PPIs do not significantly increase the risk of any of these conditions except intestinal infections. Nevertheless, we cannot exclude the possibility that PPIs might confer a small increase in the risk of developing these adverse conditions. For the treatment of GERD, gastroenterologists generally agree that the well-established benefits of PPIs far outweigh their theoretical risks."

2. Switching PPIs can be considered for patients who experience minor PPI side effects including headache, abdominal pain, nausea, vomiting, diarrhea, constipation, and flatulence.

3. For patients with GERD on PPIs who have no other risk factors for bone disease, we do not recommend that they raise their intake of calcium or vitamin D or that they have routine monitoring of bone mineral density.

4. For patients with GERD on PPIs who have no other risk factors for vitamin B12 deficiency, we do not recommend that they raise their intake of vitamin B12 or that they have routine monitoring of serum B12 levels.

5. For patients with GERD on PPIs who have no other risk factors for kidney disease, we do not recommend that they have routine monitoring of serum creatinine levels.

6. For patients with GERD on clopidogrel who have LA grade C or D esophagitis or whose GERD symptoms are not adequately controlled with alternative medical therapies, the highest quality data available suggest that the established benefits of PPI treatment outweigh their proposed but highly questionable cardiovascular risks.

7. PPIs can be used to treat GERD in patients with renal insufficiency with close monitoring of renal function or consultation with a nephrologist.

PPIs are widely considered the mainstay of medical treatment for GERD. Side effects of PPIs that have been identified in clinical trials and listed on FDA labels as the "most common adverse reactions" include headache, abdominal pain, nausea, vomiting, diarrhea, constipation, and flatulence. These relatively minor side effects occur infrequently and abate when the medications are stopped. Limited data also suggest that these side effects sometimes can be PPI preparation-specific and, for patients who experience them, a trial of switching from 1 PPI to another is a reasonable management strategy (234). Of far more concern to patients and physicians alike are the growing number of serious putative adverse effects of chronic PPI therapy that have been identified predominantly through weak associations found in observational studies (235,236).

Table 5 lists the major putative adverse effects of chronic PPI therapy and the proposed underlying mechanisms. Some of these effects are assumed to be a consequence of PPI-induced suppression of gastric acid secretion. For example, gastric acid suppression can enable ingested pathogens that ordinarily would

Table 5. Major putative adverse effects of chronic PPI therapy

Putative adverse effect	Meta-analysis reference numbers	HR[a] or OR[b] (95% CI) found in recent RCT (94)	Major proposed mechanisms
Cardiovascular events (All) MI Stroke Cardiovascular death	(237–240)	1.04[a] (0.93–1.15) 0.94[a] (0.79–1.12) 1.16[a] (0.94–1.44) 1.03[a] (0.89–1.20)	PPIs block metabolism of ADMA, which accumulates and inhibits NO synthase, thus blocking endothelial production of NO needed for vascular homeostasis
Cardiovascular events in patients on clopidogrel[c]	(241–260)	NA	PPIs are metabolized by the same enzyme needed to activate clopidogrel (CYP2C19), so concomitant use of these drugs might decrease the antiplatelet effect of clopidogrel
Kidney disease (All) AIN Chronic kidney disease	(261–265)	NA NA 1.17[b] (0.94–1.45)	AIN develops as an idiosyncratic drug reaction and progresses to chronic kidney disease
Enteric infection (other than *Clostridium. difficile*)	(266,267)	1.33[b] (1.01–1.75)	Reduced gastric acid enables ingested enteric pathogens to survive passage through the stomach
C. difficile	(268–276)	2.26[b] (0.70–7.34)	Reduced gastric acid enables survival of ingested *C. difficile* vegetative forms and prevents conversion of salivary nitrite to ROS that suppress *C. difficile* spores; PPIs may enhance *C. difficile* toxin expression and cause microbiome alterations that promote *C. difficile* colitis
SIBO	(277,278)	NA	Reduced gastric acid enables increased bacterial colonization of the UGI tract
Spontaneous bacterial peritonitis in patients with cirrhosis	(279–283)	NA	Increased bacterial colonization of the UGI tract and PPI-induced increases in UGI tract permeability predispose to bacterial translocation; PPIs also might interfere with inflammatory cell functions that ordinarily would prevent infection
Pneumonia	(284–289)	1.02[b] (0.87–1.19)	Reduced gastric acid enables UGI tract colonization with pulmonary pathogens that can be aspirated; PPIs also might interfere with inflammatory cell functions that ordinarily would prevent infection
Dementia	(290–293)	1.20[b] (0.81–1.78)	PPIs block vacuolar H^+-ATPase needed to acidify microglial lysosomes, thereby preventing their degradation of cerebral amyloid-β peptide; PPI-induced B12 deficiency also might contribute to dementia
Bone fracture	(294–302)	0.96[b] (0.79–1.17)	Reduced gastric acid causes calcium malabsorption leading to decreased bone mineral density; PPIs might reduce bone resorption by blocking vacuolar H^+-ATPase in osteoclasts; PPIs cause hypergastrinemia that might cause parathyroid hyperplasia
Gastric atrophy	(303–305)	0.73[b] (0.40–1.32)	PPIs promote corpus-predominant *H. pylori* gastritis that results in gastric atrophy with loss of parietal cells
Gastric cancer	(306–308)	NA	PPIs promote gastric atrophy and inflammation in *H. pylori*–infected patients, resulting in intestinal metaplasia predisposed to malignancy; reduced gastric acid enables overgrowth of bacteria that convert dietary nitrates to potentially carcinogenic N-nitroso compounds; PPI-induced hypergastrinemia causes gastric epithelial cell proliferation that promotes carcinogenesis
Vitamin B12 deficiency	(309)	NA	Reduced gastric acid results in malabsorption of protein-bound cobalamin; gastric atrophy results in decreased intrinsic factor production
Hypomagnesemia	(310–312)	NA	PPI effects in elevating intestinal pH may interfere with magnesium absorption, perhaps because the affinity of the enterocyte magnesium transporter TRPM6/7 for magnesium decreases in a higher pH environment
All-cause mortality	(313)	1.03[a] (0.92–1.15)	Potentially all of above

[a]Hazard ratio.
[b]Odds ratio
[c]The US Food and Drug Administration recommends avoiding the concomitant use of clopidogrel and omeprazole.
ADMA, asymmetric dimethylarginine; AIN, acute interstitial nephritis; ATP, adenosine triphosphate; CI, confidence interval; HR, hazard ratio; MI, mucosal integrity; NA, not available; NO, nitric oxide; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomized controlled trial (94); ROS, reactive oxygen species; SIBO, small intestinal bacterial overgrowth; TRPM6/7, transient receptor potential melastatin 6 and 7.

have been destroyed by gastric acid to survive and cause enteric infections or to be aspirated and cause pneumonia (236). Reduced gastric acidity can impair the uptake of certain vitamins (e.g., B12) and minerals (e.g., calcium) and can elevate serum levels of gastrin, a growth factor with proproliferative effects that might predispose to carcinogenesis (236).

Mechanisms other than gastric acid inhibition have been proposed to underlie a number of other adverse effects that have been associated with PPI usage such as kidney disease and cardiovascular events (Table 5).

One area of considerable persistent controversy relates to the association between chronic PPI use and hypomagnesemia. Two meta-analyses on this issue concluded that long-term PPI use is significantly associated with hypomagnesemia (310,314), whereas another 2 concluded that the risk of PPI-induced hypomagnesemia was unclear because of significant heterogeneity among studies (311,312). A recent AGA Best Practice Recommendation concluded that long-term PPI users should not routinely screen or monitor serum magnesium levels (315), whereas the FDA suggests that health care providers should consider monitoring magnesium levels before initiation of PPI treatment and then periodically (http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm). We feel that presently there are insufficient data to make a meaningful recommendation regarding the need for monitoring of magnesium levels in patients on chronic PPI therapy.

It is important to appreciate that the mere identification of an association between PPIs and adverse conditions in observational studies cannot establish a cause-and-effect relationship and that such studies are highly susceptible to biases that can prejudice results. Observational studies on potential PPI side effects are especially susceptible to the biases of confounding by indication (in which the medical indication for a PPI, not the PPI itself, is responsible for the adverse effect) and protopathic bias (in which the PPI does not cause an adverse condition, but is prescribed to treat symptoms of that already-present yet unrecognized condition) (316,317).

The epidemiologist/statistician Sir Austin Bradford Hill, in his Presidential Address to the Section of Occupational Medicine of the Royal Society of Medicine in 1965, proposed 9 criteria that can strengthen the case for a cause-and-effect relationship in associations between exposures and diseases identified through observational studies (318). These so-called Bradford-Hill criteria include (i) strength of the association, (ii) consistency of the observation, (iii) specificity of the exposure for the disease, (iv) temporality (i.e., exposure preceded disease), (v) biological gradient (dose–response), (vi) plausibility of the proposed mechanism for how the exposure might cause disease, (vii) coherence among epidemiologic and other types of data, (viii) experimental data support a cause-and-effect relationship, and (ix) analogy with the effects of similar types of exposures. In 2017, Vaezi et al. (319) reported that no proposed PPI adverse effect fulfilled all 9 of the Bradford-Hill criteria, and most fulfilled fewer than 4.

It has been noted that most reported associations in observational clinical research are spurious, and the minority that are real are often exaggerated (320). Experts caution that weak associations found in such studies are more likely to result from bias than from cause-and-effect relationships and, unless RRs in cohort studies exceed 2–3 or ORs in case-control studies exceed 3–4, the findings generally should not be considered credible (320). Reports of observational studies that have identified potential PPI side effects typically have described weak associations with RRs or ORs < 2 (261). Furthermore, even strong associations in such studies do not establish cause-and-effect relationships. For example, some observational studies have found a strong association (ORs > 4) between PPI usage and esophageal adenocarcinoma, an

association that is likely due to confounding by indication (i.e., PPIs were prescribed to treat GERD, which was the real risk factor for the cancer that subsequently developed) (321). Observational studies also have found a strong association between PPI usage and development of community-acquired pneumonia, an association that may well have been the result of protopathic bias (i.e., PPIs were prescribed for symptoms of cough and chest discomfort that were mistakenly attributed to GERD but in fact were caused by an unrecognized, early pneumonia) (322).

A recent, large, placebo-controlled randomized trial reported by Moayyedi et al. (323) has shed considerable light on the issue of PPI safety. In this exceptionally high-quality study, 17,598 patients aged 65 years or older with stable cardiovascular or peripheral artery disease treated with rivaroxaban and/or aspirin were randomly assigned to receive the PPI pantoprazole (40 mg daily, n = 8,791) or placebo (n = 8,807). After randomization, data were collected at 6-month intervals over a period of 3 years specifically with the intent of identifying potential PPI side effects including pneumonia, *Clostridium difficile* infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, dementia, cardiovascular disease, cancer, and all-cause mortality. The investigators found no significant differences between the PPI and placebo groups in rates of occurrence for any of those potential side effects except for enteric infections (1.4% vs 1.0% in the PPI and placebo groups, respectively; OR 1.33; 95% CI, 1.01–1.75). Table 5 lists the hazard ratios (HRs) and ORs for all the putative adverse events evaluated in this study. The authors concluded that the use of pantoprazole for 3 years was not associated with any adverse event other than a modestly increased risk of developing enteric infections.

Moayyedi's report provides high-quality evidence to suggest that most of the associations between PPI usage and adverse events that have been identified in observational studies were the result of residual confounding and other biases and unlikely to represent cause-and-effect relationships. Reassuring as this study is, it is important to consider several caveats. First, the trial had a maximum follow-up of 5 years, which might not be sufficient time for some adverse events to develop (e.g., gastric cancer) (324). Next, despite the large size of the study, some adverse events (e.g., gastric atrophy and *C. difficile*–associated diarrhea) occurred so infrequently that conclusions regarding possible PPI involvement are limited. Finally, and perhaps most important, the 95% CIs around some of the HRs and ORs observed in this prospective trial, large as it is, still are relatively wide. It is reassuring that the HRs and ORs for some events (pneumonia, fracture, cardiovascular disease, dementia, and all-cause mortality) are even lower than the lower limits of the 95% CIs reported in earlier observational studies. Nevertheless, this study cannot exclude the possibility that PPIs confer a modest risk of any of these adverse events (i.e., the upper limit of the 95% CIs all are >1), and even a modest risk of such serious events is cause for concern. As the authors themselves acknowledge, the possibility that PPIs confer a modest risk of these putative adverse events can never be excluded no matter how large the study sample size (323).

SUMMARY

We have made every effort to review and grade all available evidence to develop this guideline. Much is new and different

compared with the 2013 guideline, particularly because it relates to approaching extraesophageal symptoms, refractory GERD, and surgical and endoscopic therapies. Each section provides a separate review of the evidence supporting our recommendations; therefore, some repetition was necessary to do this effectively. Our algorithms offer an overall approach to diagnosis and management of the major presentations of the disease and reflect our discussion in the body of the article. We have attempted to address all the key issues in PPI management and adverse events, so clinicians will have a comprehensive, go-to source in the guideline. We have performed our best to present a thorough review of the evidence for our recommendations and key concepts and to provide an evidence-based approach to GERD that can be used effectively in everyday practice.

We expect that new diagnostic tools and treatments will be developed and those that we have will be further refined. Mucosal integrity testing, e.g., is available commercially but is not developed sufficiently to warrant discussion in this guideline. Esophageal function testing is addressed in detail in another guideline, whereas other extensive reviews focus on valuable additions to our clinical armamentarium such as MSA and TIF. Potassium-competitive acid blockers are exciting potential new agents for pharmacologic treatment of GERD. One, currently available in Japan, presently is undergoing phase 3 trials in the United States as we complete this document and may well be approved for clinical use soon after this review is published. Future research with advanced endoscopic techniques, data on long-term efficacy of surgical intervention, and advances in artificial intelligence and basic science will almost certainly change the way we manage GERD going forward.

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