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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on the Diagnosis and Management of Extraesophageal Gastroesophageal Reflux Disease: Expert Review

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DESCRIPTION: **The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update is to review the available evidence and expert advice regarding the clinical management of patients with suspected extraesophageal gastroesophageal reflux disease.**

METHODS: **This article provides practical advice based on the available published evidence including that identified from recently published reviews from leading investigators in the field, prospective and population studies, clinical trials, and recent clinical guidelines and technical reviews. This best practice document is not based on a formal systematic review. The best practice advice as presented in this document applies to patients with symptoms or conditions suspected to be related to extraesophageal reflux (EER). This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the CPUC and external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*. These Best Practice Advice (BPA) statements were drawn from a review of the published literature and from expert opinion. Because systematic reviews were not performed, these BPA statements do not carry formal ratings of the quality of evidence or strength of the presented considerations.**

BEST PRACTICE ADVICE 1: **Gastroenterologists should be aware of potential extraesophageal manifestations of gastroesophageal reflux disease (GERD) and should inquire about such disorders including laryngitis, chronic cough, asthma, and dental erosions in GERD patients to determine whether GERD may be a contributing factor to these conditions.**

BEST PRACTICE ADVICE 2: **Development of a multidisciplinary approach to extraesophageal (EER) manifestations is an important consideration because the conditions are often multifactorial, requiring input from non-gastroenterology (GI) specialties. Results from diagnostic testing (ie, bronchoscopy, thoracic imaging, laryngoscopy, etc) from non-GI disciplines should be taken into consideration when gastroesophageal reflux (GER) is considered as a cause for extraesophageal symptoms.**

BEST PRACTICE ADVICE 3: **Currently, there is no single diagnostic tool that can conclusively identify GER as the cause of EER symptoms. Determination of the contribution of GER to EER symptoms should be based on the global clinical impression derived from patients' symptoms, response to GER therapy, and results of endoscopy and reflux testing.**

BEST PRACTICE ADVICE 4: **Consideration should be given toward diagnostic testing for reflux before initiation of proton pump inhibitor (PPI) therapy in patients with potential extraesophageal manifestations of GERD, but without typical GERD symptoms. Initial single-dose PPI trial, titrating up to twice daily in those with typical GERD symptoms, is reasonable.**

Abbreviations used in this paper: BPA, best practice advice; CI, confidence interval; EER, extraesophageal reflux; EGD, esophagogastroduodenoscopy; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; H2RA, histamine 2 receptor antagonist; LPR, laryngopharyngeal reflux; PPI, proton pump inhibitor; UES, external upper esophageal sphincter.

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BEST PRACTICE ADVICE 5: **Symptom improvement of EER manifestations while on PPI therapy may result from mechanisms of action other than acid suppression and should not be regarded as confirmation for GERD.**

BEST PRACTICE ADVICE 6: **In patients with suspected extraesophageal manifestation of GERD who have failed one trial (up to 12 weeks) of PPI therapy, one should consider objective testing for pathologic GER, because additional trials of different PPIs are low yield.**

BEST PRACTICE ADVICE 7: **Initial testing to evaluate for reflux should be tailored to patients' clinical presentation and can include upper endoscopy and ambulatory reflux monitoring studies of acid suppressive therapy.**

BEST PRACTICE ADVICE 8: **Testing can be considered for those with an established objective diagnosis of GERD who do not respond to high doses of acid suppression. Testing can include pH-impedance monitoring while on acid suppression to evaluate the role of ongoing acid or non-acid reflux.**

BEST PRACTICE ADVICE 9: **Alternative treatment methods to acid suppressive therapy (eg, lifestyle modifications, alginate-containing antacids, external upper esophageal sphincter compression device, cognitive-behavioral therapy, neuromodulators) may serve a role in management of EER symptoms.**

BEST PRACTICE ADVICE 10: **Shared decision-making should be performed before referral for anti-reflux surgery for EER when the patient has clear, objectively defined evidence of GERD. However, a lack of response to PPI therapy predicts lack of response to anti-reflux surgery and should be incorporated into the decision process.**

Keywords: Extraesophageal Reflux; Gastroesophageal Reflux; Laryngopharyngeal Reflux; Endoscopy; Ambulatory Reflux Monitor; Laryngoscopy.

Gastroesophageal reflux disease (GERD) is increasing in prevalence, and this, in turn, implores increased investigation into its extraesophageal manifestations. Extraesophageal reflux (EER) is a subset of gastroesophageal reflux (GER) that leads to troublesome symptoms/conditions that are not normally attributed to the esophagus. Diagnostic algorithms for EER are difficult because the manifestations of EER are heterogeneous and often overlap with other conditions. The healthcare burden of EER is great because of the lack of a gold standard diagnostic test, poor responsiveness to proton pump inhibitor (PPI) therapy, and delay in recognition.[1–4]

The concept of extraesophageal symptoms secondary to GERD is complex and often controversial, leading to diagnostic and therapeutic challenges. Several extraesophageal symptoms have been associated with GERD, although the strength of evidence to support a causal relation varies. Possible extraesophageal manifestations of GERD include cough, laryngeal hoarseness, dysphonia, pulmonary fibrosis, asthma, dental erosions/caries, sinus disease, ear disease, post-nasal drip, and throat clearing (Table 1). Patients with EER may not complain of heartburn or regurgitation; thus, the onus may lie on the clinician to determine whether acid reflux is a contributing factor of the symptoms. Causation (as opposed to association) is a difficult assessment because many conditions thought to be related to EER are associated with a higher incidence of acid reflux.[2]

The difficulties in confirming a causal association between reflux and EER symptoms relate to variable responses to PPI therapy. Additional controversy arises over whether fluid refluxate causes damage leading to EER, whether the fluid needs to be acidic or merely contain pepsin, or whether neurogenic signaling leads to inflammation and subsequent symptoms.[5,6] Thus, a simple trial of PPI may not provide accurate diagnostic information regarding the contribution of acid reflux to EER symptoms.

Herein we will discuss conditions suspected to have potential relationships to acid reflux and best approaches to diagnosis, evaluation, and therapy.

Conditions in Which EER Is Suspect

Best Practice Advice 1: Gastroenterologists should be aware of potential extraesophageal manifestations of gastroesophageal reflux disease (GERD) and should inquire about such disorders including laryngitis, chronic cough, asthma, and dental erosions in GERD patients to determine whether GERD may be a contributing factor to these conditions.

Best Practice Advice 2: Development of a multidisciplinary approach to extraesophageal (EER) manifestations is an important consideration because the conditions are often multifactorial, requiring input from non-gastroenterology (GI) specialties. Results from diagnostic testing (ie,

Table 1. Different Postulated Manifestations of EER

Extraesophageal symptoms and manifestations	Differential diagnosis	Multidisciplinary team
Laryngeal/ENT	Postnasal drip	Otolaryngology
Laryngitis/hoarseness	Laryngeal allergy	Gastroenterology
Globus	Functional dysphonia	Allergy/Immunology
Mucus in throat	Laryngeal papilloma	Speech pathology
Throat clearing	Muscle tension dysphonia	Behavioral psychology
Throat pain	Vocal cord paralysis	
Sinus inflammation	Vocal cord polyps	
Post-nasal drip	Sinusitis (occult)	
	Gastric inlet patch	
Pulmonary	Post-nasal drip	Pulmonology
Asthma	Asthma	Otolaryngology
Chronic cough	Vocal cord dysfunction	Allergy/Immunology
Pulmonary fibrosis	Medication reaction (ie, angiotensin converting enzyme inhibitors)	Gastroenterology
Allograft failure	Lung transplant rejection	Primary care
Dentition	Poor dietary habits (ie, acidic soft drinks, fruit juices)	Dentistry
Dental erosions	Eating disorders with regurgitation (bulimia)	Gastroenterology
Dental caries	Xerostomia (Sjogren's)	Nutrition
	Environmental (ie, around acidic fumes)	Primary care
		Psychology

NOTE. Gastroenterologists should keep in mind all possible non-EER contributions to the symptoms and the potential multidisciplinary teams for collaborative evaluation.

bronchoscopy, thoracic imaging, laryngoscopy, etc) from non-GI disciplines should be taken into consideration when gastroesophageal reflux (GER) is considered as a cause for extraesophageal symptoms.

Most disorders suspicious for EER are often seen by specialties outside of gastroenterology such as pulmonary, otolaryngology, and dentistry. Patients with EER will commonly see many different physicians and undergo a multitude of testing without a final conclusive determination. A multidisciplinary approach with communication between all treating disciplines results in the best outcomes for suspected EER patients. Common disorders thought to have an association with EER are chronic cough, laryngeal hoarseness, dysphonia, pulmonary fibrosis, asthma, dental erosions, sinus disease, ear disease, post-nasal drip, voice dysphonia, and throat clearing. Table 1 lists conditions commonly attributed to EER, alternative diagnoses, and the multidisciplinary teams that can contribute to patient workup and management.

Multiple respiratory conditions are postulated to be related to gastroesophageal reflux. The impact of esophageal dysfunction on pulmonary and laryngeal disorder is likely related to 2 different mechanisms: the reflux pathway leading to micro-aspiration and the reflex pathway triggering vagally mediated airway reactions.[6] In the reflux pathway, EER can exacerbate inflammatory conditions via acid or non-acid mechanisms, including micro-aspiration of other digestive fluids. In such situations, symptom improvement may not be seen with acid suppression. In the reflex pathway, EER may contribute to the pathology of supra-esophageal complaints by increasing laryngeal or airway inflammation via neurologic mechanisms.[7–9] Further confusing the picture, conditions associated with EER (such as chronic cough) may cause GERD or increase reflux episodes.[10] Approaching these conditions with such knowledge will enable a more comprehensive approach to evaluation and management between disciplines. Ultimately, a large differential of possible EER syndromes should be entertained because EER may only be a part of the equation.[11] Table 1 includes potential manifestations of EER, a non-exhaustive list of non-EER/non-gastroenterology differential diagnoses, and potential multidisciplinary teams for collaborative evaluation.

Diagnostic Testing for EER

Best Practice Advice 3: Currently, there is no single diagnostic tool that can conclusively identify GER as the cause of EER symptoms. Determination of the contribution of GER to EER symptoms should be based on the global clinical impression derived from patients' symptoms, response to GER therapy, and results of endoscopy and reflux testing.

Although various diagnostic tests are available to evaluate GERD, there is not a single gold standard test for the diagnosis of EER. Instead, a diagnosis of EER requires incorporating the global clinical evaluation involving patients' symptoms, endoscopic findings, esophageal reflux monitoring, and response to treatments.[1,12] Further adding to the challenge is that there is limited accuracy of tests when it comes to determining the causal association of GERD and

extraesophageal symptoms. Pragmatically, the exclusion of GERD decreases the chance that extraesophageal symptoms are caused by GERD. On the other hand, if a GERD diagnosis can be objectively supported, the possibility remains that GERD may be a causal factor for symptoms. Recognizing the potential pros and cons of various diagnostic tests facilitates their application to diagnosing GERD and attributing GERD to extraesophageal symptoms. Determination of GERD contribution should be personalized to the individual patient and should take into account patient symptoms, response to GERD treatment, and objective evidence of GERD on endoscopic or reflux testing.

PPI Trial

Best Practice Advice 4: Consideration should be given toward diagnostic testing for reflux before initiation of proton pump inhibitor (PPI) therapy in patients with potential extraesophageal manifestations of GERD, but without typical GERD symptoms. Initial single-dose PPI trial, titrating up to twice daily, in those with typical GERD symptoms is reasonable.

Best Practice Advice 5: Symptom improvement of EER manifestations while on PPI therapy may result from mechanisms of action other than acid suppression and should not be regarded as confirmation for GERD.

The limitations of an empiric PPI trial in diagnosis of EER are due to the inconsistent therapeutic response of EER-associated syndromes to PPI (pharmacologic management). A meta-analysis demonstrated sensitivity of 71%–78% and specificity of 41%–54% for an empiric PPI trial (as compared with esophagitis on endoscopy or ambulatory pH monitoring) among patients with classic reflux symptoms of heartburn and regurgitation.[13] Considering the greater variation expected with PPI response for extraesophageal symptoms, the diagnostic performance of empiric PPI trial for a diagnosis of EER would be anticipated to be substantially lower. Furthermore, symptom response to PPI suggests reflux as a contributor; however, this should not be taken as confirmation of GERD because of possible placebo effects.[14] With potential drawbacks of PPI (costs, rare adverse events) and limited evidence for a PPI trial for diagnosing GERD-related EER, consideration should be given for early reflux testing instead of empiric PPI therapy in patients without typical reflux symptom (Figure 1). Thus, although there is clinical value in incorporating response to PPI treatment, its isolated application does not support or refute an EER diagnosis or long-term treatment.

Esophagogastroduodenoscopy (EGD) and laryngoscopy have limited roles in the diagnosis of EER (see Supplementary Material).

Ambulatory Esophageal Reflux Monitoring

Best Practice Advice 6: In patients with suspected extraesophageal manifestation of GERD who have failed one trial (up to 12 weeks) of PPI therapy, one should consider objective testing for pathologic GER, because additional trials of different PPIs are low yield.

Best Practice Advice 7: Initial testing to evaluate for reflux should be tailored to patients' clinical presentation and can include upper endoscopy and ambulatory reflux monitoring studies of acid suppressive medications.

Best Practice Advice 8: Testing can be considered for those with an established objective diagnosis of GERD who do not respond to high doses of acid suppression. Testing can include pH impedance monitoring while on acid suppression to evaluate the role of ongoing acid or non-acid reflux.

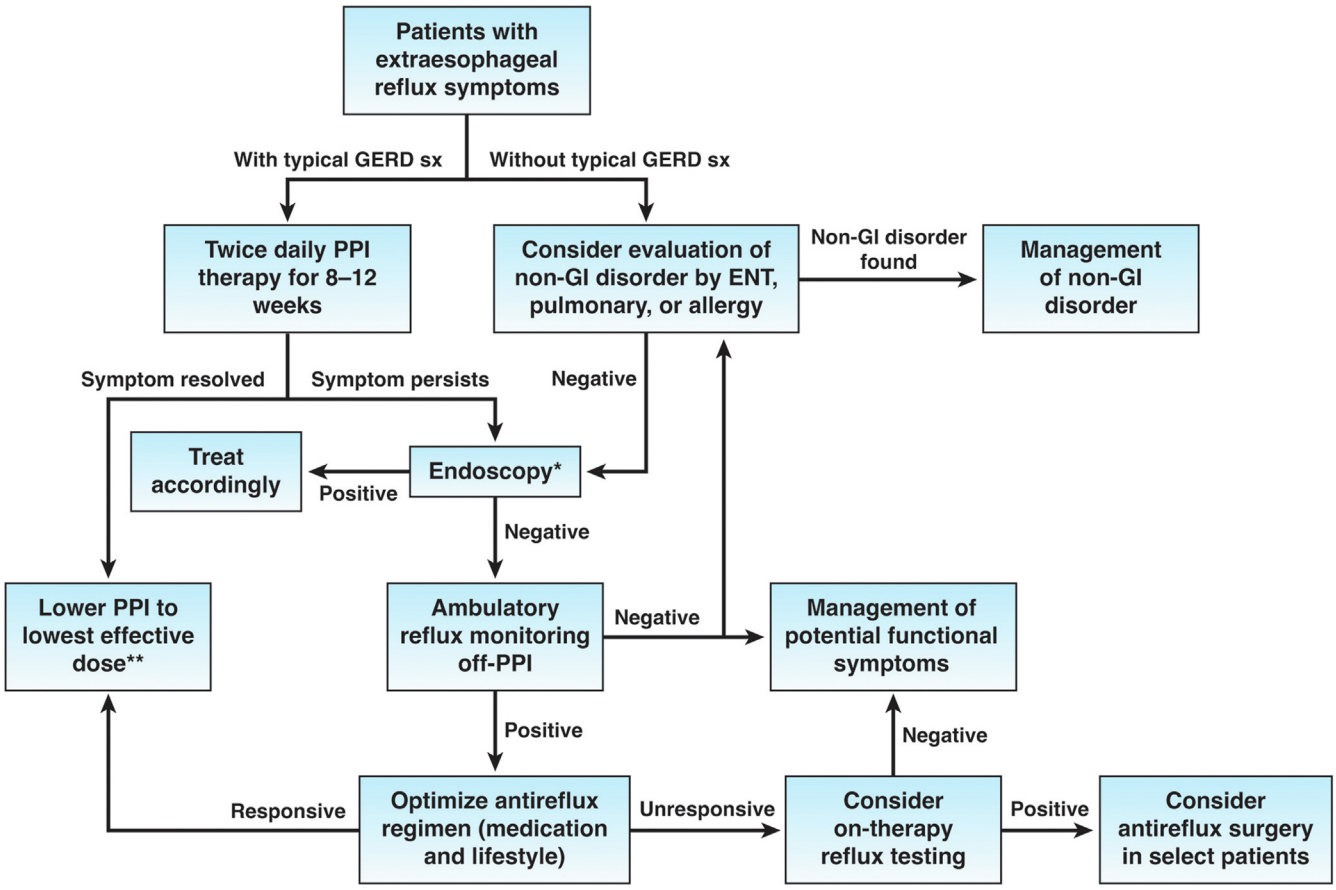
Ambulatory esophageal reflux monitoring provides a method to quantitate esophageal reflux burden to facilitate an objective GERD diagnosis, particularly in the setting of non-erosive reflux disease. Recent recommendations toward ambulatory reflux testing before initiation of empiric pharmacotherapy in patients with EER symptoms were guided by the fact that 50%–60% of patients with EER symptoms will not have GERD and will not respond to anti-reflux therapies, as well as cost-effective studies favoring early testing with reflux monitoring over empiric PPI trial in EER.[15–17] Several modalities are available for ambulatory esophageal reflux monitoring that include a catheter-based pH sensor, pH impedance, or wireless pH capsule (Table 2). Each testing modality, as well as testing on or off acid suppressive therapy, offers advantages and disadvantages in clinical practice (see Supplementary Material).

Ambulatory esophageal pH monitoring objectively defines reflux burden to facilitate a GERD diagnosis but does not determine if GERD is the cause of extraesophageal symptoms. Whichever the reflux testing modality, the strongest confidence for EER is achieved after ambulatory reflux testing showing pathologic acid exposure and a positive symptom-reflux association for EER symptoms. The pH impedance monitoring can detect weakly acidic and non-acidic reflux episodes (in addition to acid reflux), as well as proximal reflux episodes, which may cause extraesophageal symptoms by direct acid-mucosal contact. Notably, ambulatory reflux monitoring for the evaluation of GERD in the presence of extraesophageal symptoms should be performed off acid suppressive therapy, unless previous objective evidence (eg, positive pH test) for GERD exists (Figure 1).

Treatment of EER

Best Practice Advice 9: Alternative treatment methods to acid suppressive therapy (eg, lifestyle modifications, alginate-containing antacids, external upper esophageal sphincter compression device, cognitive-behavioral therapy, neuromodulators) may serve a role in management of EER symptoms.

Treatment of esophageal and extraesophageal GERD aims to achieve and maintain symptom relief, heal



*Look for evidence of GERD-related injury or complications and rule out alternative esophageal diseases
**Consider endoscopy and reflux monitoring to support long-term use of PPI

Figure 1. Algorithm for the evaluation of suspected EER. An empiric PPI trial can be considered in patients with extra-esophageal and concurrent typical reflux symptoms, whereas early reflux testing should be considered in those with extra-esophageal symptoms alone. To avoid long-term PPI use for a placebo effect, patients responsive to a trial of PPI should be titrated to the lowest effective dose and should be considered for off-therapy endoscopy or reflux testing. In patients without typical reflux symptoms or those with negative reflux workup, early involvement of multidisciplinary services should be considered. GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; Sx, symptoms.

mucosal damage, and prevent complications. Treatment strategies include lifestyle measures, pharmacologic management of reflux through alginates or acid suppression, a device to prevent supra-esophageal reflux by bolstering the upper esophageal sphincter, and surgical/endoscopic approaches to augment the anti-reflux barrier at the level of the lower esophageal sphincter. Ascertaining the effectiveness of EER therapies is challenging, because in the absence of a gold standard diagnostic test that can reliably identify patients in whom extraesophageal symptoms are due to GERD, clinical trials may often include patients in whom GERD is not the cause of the symptoms, and in whom consequently therapy will fail. Furthermore, there is

Table 2. Modalities of Ambulatory Esophageal Reflux Monitoring

	pH impedance	pH catheter	Wireless pH capsule
Standard distal pH sensor positioning	5 cm proximal to LES (manometrically identified)	5 cm proximal to LES (manometrically identified)	6 cm proximal to SCJ (endoscopically identified)
Test duration	24 hours	24 hours	48–96 hours
Test setting	Placed in awake patient	Placed in awake patient	Typically placed during sedated endoscopy
Reflux composition detected	Acidic, weak-acidic, non-acidic	Acidic	Acidic
Proximal reflux detected?	Yes	Possible	No

LES, lower esophageal sphincter; SCJ, squamocolumnar junction.

heterogeneity among EER studies in patient inclusion criteria and lack of gold standards for testing and treatment regimens and endpoints.[18–20] These issues may in part explain the limited response to treatment in the studies that are discussed in this section.

Lifestyle Measures

Lifestyle modification measures including avoidance of refluxogenic foods, food avoidance for at least 2–3 hours before recumbency, positional changes during the sleep period, and weight loss have been proposed for management of GERD.[1] Late evening meals have been shown to contribute to reflux.[21] Head of bed elevation as well as left lateral decubitus position have been shown to improve nocturnal esophageal acid exposure.[22–24] Obesity was significantly associated with reflux symptoms and erosive esophagitis in a meta-analysis,[25] and weight loss was associated with a reduction in symptoms and esophageal acid exposure.[21] The data regarding avoidance of presumably refluxogenic foods (eg, chocolate, coffee, alcohol) in EER are limited, and therefore avoidance of trigger foods on a patient-by-patient basis is a more reasonable practice. In summary, avoidance of food intake before recumbency, elevating the head of the bed, the left lateral decubitus position for sleeping, and weight loss are all reasonable treatments for EER. Data on dietary avoidance in EER are limited, although avoidance of foods that consistently and predictably lead to worsening of symptoms should be considered.

Pharmacologic Management

Acid suppression therapy. Acid suppression with PPIs is the mainstay of pharmacologic therapy for GERD, and multiple randomized controlled trials have shown the effectiveness of these medications for healing of erosive esophagitis and controlling typical symptoms of GERD such as heartburn and regurgitation.[1] However, similar effectiveness has not been shown by meta-analyses assessing PPI therapy for EER, even though some uncontrolled trials suggest a role for PPIs in these patients.[18] A meta-analysis of 8 randomized controlled trials found no advantage for PPIs over placebo for the treatment of suspected GERD-related chronic laryngitis (relative risk, 1.28; 95% confidence interval [CI], 0.94–1.74).[26] Similarly, a meta-analysis of 5 placebo-controlled studies found no clear benefit for PPIs compared with placebo for treatment of chronic cough.[27] Furthermore, a meta-analysis of 11 placebo-controlled studies evaluating PPI therapy to treat asthma found that these medications resulted in a statistically significant improvement in morning peak expiratory flow that was unlikely to be clinically meaningful when compared with placebo (mean difference, 8.68 L/min; 95% CI, 2.35–15.02), and therefore empirical use of PPIs for routine asthma treatment was not endorsed.[28]

Twice daily PPI is superior to once daily PPI in gastric acid suppression and likely more effective for EER symptoms. In a prospective cohort study comparing twice daily with once daily PPI in patients with EER symptoms, a higher response rate was seen in those on twice daily than once daily PPI, and 54% of patients who did not respond to once daily PPI had symptom improvement after an additional 8 weeks of twice daily PPI.[29] A 2- to 3-month trial of PPI is considered optimal treatment in patients with EER symptoms.[30] It is important to keep in mind that patients with objectively documented GERD and EER symptoms may fail PPI therapy for various reasons: (1) true PPI failure with ongoing acid reflux, (2) adequate acid suppression but ongoing non-acid or weakly acidic reflux, or (3) the presence of additional non-GERD factors contributing to their symptoms even though GERD may be adequately controlled.

In summary, PPI therapy (up to twice daily dosing for 8–12 weeks in empiric treatment) to address extra-esophageal symptoms should be considered in patients with concomitant EER and esophageal reflux symptoms, or in those with pathologic reflux documented through objective testing. In patients with EER symptoms alone, there is no clear evidence for empiric PPI therapy. Non-PPI treatment options including alginate-containing antacids, neuromodulators, cognitive behavioral therapy, and hypnotherapy may have a role in reducing EER symptoms, although more robust data are needed (Supplementary Material).

Upper Esophageal Sphincter Augmentation

An external upper esophageal sphincter (UES) compression device has been recently developed; it applies 20–30 mmHg of cricoid pressure, resulting in increased intraluminal UES pressure and thus enhancing this barrier to supraesophageal reflux. An early uncontrolled study of 15 patients suggested that laryngeal symptoms may improve with the use of this device.[31] A more recent study of 31 patients with laryngeal symptoms reported symptom improvement in 31% after a 4-week course of PPI, and this increased to 55% after the UES compression device was added to PPI.[32] Although not currently widely available for clinical use, UES compression device may be useful for reduction of certain EER symptoms.

Surgical and Endoscopic Therapies

Best Practice Advice 10: Shared decision-making should be performed before referral for anti-reflux surgery for EER when the patient has clear, objectively defined evidence of GERD. However, a lack of response to PPI therapy predicts lack of response to anti-reflux surgery and should be incorporated into the decision process.

The data addressing surgical management of EER do not show a robust response to this type of intervention. A

systematic review of observational data including 27 articles showed variable effectiveness of antireflux surgery in management of cough or laryngeal symptoms.[33] Another systematic review of 34 observational studies was inconclusive regarding whether fundoplication is effective for treatment of laryngopharyngeal reflux.[34] Syndromes of chronic cough, laryngopharyngeal reflux, and asthma might improve after antireflux surgery only in highly selected patients.[33] The existing data are generally of low quality, and no randomized controlled trials comparing antireflux surgery with medical therapy in the treatment of cough or laryngopharyngeal reflux exist to date. These results bring up the question as to which patients, if any, may benefit from antireflux surgery to treat EER. A retrospective study of 36 patients treated with fundoplication for EER found that response to PPI therapy before operation was associated with effectiveness of surgery.[35] Overall, effectiveness of antireflux surgery was found to be less predictable in patients with extraesophageal symptoms of GERD than in patients with typical GERD. In patients unresponsive to acid suppression, the presence of heartburn and a high burden of acid reflux (acid exposure time >12%) may predict response to surgery.[36] Studies are needed to make meaningful conclusions about magnetic sphincter augmentation or endoscopic therapies for GERD. As such, surgery should only be considered in highly selected patients with EER, such as those with concomitant heartburn/regurgitation, a prior response to PPI, and a high burden of acid reflux demonstrated by pH monitoring. Fundoplication should only be undertaken after careful consideration of benefits, risks, and alternatives, in a shared decision-making process between the clinicians and the patient.

Despite the high prevalence of GERD in laryngitis, asthma, and cough, a known, direct causal link for all patients is lacking, and not all patients with GERD have reflux-induced extraesophageal symptoms. Unfortunately, our current armamentarium of diagnostic tests lacks specificity and sensitivity. The results of antireflux therapy on pulmonary outcomes are inconsistent and contradictory. Information gaps persist in the diagnosis and evaluation of EER and conditions associated with EER. Gastroenterologists continue to receive referrals for possible GERD-related cough, asthma, and laryngitis. Educating gastroenterology clinicians about the pitfalls of diagnostic algorithms and therapies will empower them to expand this knowledge to patients, potentially avoiding inappropriate use of acid suppression for conditions that may not be minimally (or entirely) related to acid reflux. Patients with extraesophageal symptoms are often left without a clear diagnosis after consultation with multiple specialized providers. A patient handout including answers to frequently asked questions can help with patient understanding and set expectations before gastroenterology investigations (Supplementary Figure 1). Shared decision-making is pivotal in optimizing outcomes for all possible approaches to EER because currently diagnostic and therapeutic algorithms are likely confounded by concurrent comorbid conditions.

Supplementary Material

Note: to access the supplementary materials accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org and at https://doi.org/10.1016/j.cgh.2023.01.040.

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Conflicts of interest
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Supplementary Material

Diagnostic Testing for EER

Esophagogastroduodenoscopy

EGD is typically the initial diagnostic test performed for the evaluation of esophageal symptoms, particularly when alarm symptoms (eg, dysphagia) are present or if there is a lack of initial response to treatment.[1] EGD (ideally performed after holding PPI for 2–4 weeks to increase diagnostic yield for esophagitis) provides evaluation for objective mucosal abnormalities associated with GERD and contributing factors (eg, hiatal hernia) and exclusion of alternate diagnoses (eg, gastric inlet patch, eosinophilic esophagitis, fungal esophagitis). Whereas objective GERD findings including erosive esophagitis (Los Angeles grades B, C, D) or long-segment Barrett's esophagus are considered highly specific for GERD, EGD in the majority of patients with GERD will be normal.[2] In addition, EGD findings do not confirm that the extraesophageal symptoms are in fact caused by reflux.[3] As such, EGDs should be performed for assessment of presence of GERD injury/complications but not as a diagnostic tool for confirmation of GERD or to conclude on a causal link between extraesophageal symptoms and GERD.

Laryngoscopy

Otolaryngologist evaluation with laryngoscopy is often used in the evaluation of extraesophageal symptoms, with findings such as erythema or edema of the arytenoids or vocal folds sometimes attributed to EER. However, these findings can be observed in asymptomatic volunteers, can be caused by etiologies other than GERD, and there may be inconsistencies in assessing these findings between raters.[4–6] In addition, there are inconsistent relationships between laryngoscope abnormalities and objective esophageal reflux monitoring.[7,8] Diagnosis of EER by laryngoscopy alone lacks specificity to identify GERD as an etiology for extraesophageal symptoms. Many individual signs thought to be related to reflux (laryngeal edema or erythema, posterior pharyngeal wall pachydermia, vocal process granuloma, etc) are present in non-reflux patients.[9–11] However, laryngoscopy is often used to identify alternative diagnoses responsible for the extraesophageal symptoms. Scoring systems have been proposed using laryngopharyngoscopy findings for diagnosis of EER including the Reflux Finding Score and Reflux Sign Assessment. The success of these efforts remains a subject of debate, with concerns for inter- and intra-rater reliability, correlation of physical findings with patient-reported symptoms, and correlation of findings with response to treatment.[12]

Ambulatory Reflux Testing Modalities

Traditional pH-metry focuses on esophageal acid exposure time and reflux events (both quantified relative to an intraluminal pH <4) at the distal esophageal pH sensor. Although this defines the presence (or absence) of abnormal esophageal reflux burden to support (or refute) a GERD diagnosis, distal esophageal pH monitoring has not consistently predicted response of EER manifestations with reflux treatments.[13–16]

Although limited by distal pH monitoring for extraesophageal symptoms, wireless pH monitoring offers the advantages of allowing for a longer monitoring period (up to 96 hours) than catheter-based 24-hour pH-only reflux monitoring and allows for assessment of day-to-day variability in reflux.[17,18] This may potentially increase the diagnostic yield for detection of pathologic acid exposure (which conversely can be applied as providing a high negative predictive value for GERD if acid reflux parameters are normal over the extended monitoring period). In addition to the benefit of prolonged pH monitoring, the wireless monitor provides greater patient tolerance, which allows for reflux monitoring to occur without altering one's normal daily life substantially.[18,19]

The pH-impedance catheters incorporate multiple intraluminal impedance channels along the length of the catheter. Intraluminal impedance facilitates additional characterization of reflux events by assessing their contents (air and/or liquid) and composition (acidic: pH <4, weak-acidic pH 4–7, or non-acidic pH >7). Because weak and non-acid reflux have been associated with extraesophageal symptoms, particularly chronic cough, this represents an advantage for pH-impedance testing for patients with extraesophageal symptoms.[20–22]

Catheter-based reflux monitoring with dual sensors can also assess for proximal reflux events via a second pH sensor positioned in the proximal esophagus (in catheters with or without impedance) or by assessment of proximal extent of reflux events using impedance in pH-impedance monitoring. Evaluation of proximal esophageal reflux conceptually provides an advantage to determine a causal relationship of reflux with extraesophageal symptoms; however, its application is limited by a lack of well-established thresholds from which to identify clinically relevant, "pathologic" proximal reflux.[23–25]

Other Testing Modalities

Measurement of acid or reflux contents in the oropharynx, via oropharyngeal pH monitoring or salivary pepsin assays, respectively, represents conceptually appealing methods to facilitate diagnosis EER. Both demonstrate their potential utility to diagnose GERD, including among patients with extraesophageal symptoms.[8,26–30] However, other studies assessing salivary pepsin assay and oropharyngeal pH have demonstrated poor concordance with esophageal reflux monitoring as well as overlap in results between healthy, asymptomatic volunteers (controls) and symptomatic patients.[26,31–35] Overall, this limits enthusiasm for application of these technologies in clinical practice. Therefore,

tests measuring oropharyngeal pH or salivary pepsin are currently unlikely to be sufficiently reliable or accurate in the evaluation of EER.

Treatment of EER

Non-PPI Treatment Options

Histamine 2 receptor antagonists (H2RA) are inferior to PPIs in efficacy to reduce acid production, and their use is further limited by tachyphylaxis with frequent repeated use. However, H2RA have been shown to improve nighttime reflux for patients on PPI therapy.[36] Use of H2RA in EER is therefore limited to need for a faster onset of action therapy and for control of nocturnal breakthrough reflux in patients already on PPI.

Alginate. Alginate, a polysaccharide derived from seaweed, forms a viscous raft that can function as a barrier to reflux in part by neutralizing the acid pocket in the proximal stomach.[37] A randomized trial showed that in patients with laryngopharyngeal reflux (LPR), alginate resulted in significant improvement of symptoms and laryngeal signs compared with no treatment, but it is important to note that there was no placebo arm.[38] In a more recent double-blind, placebo-controlled trial in patients with LPR, symptom improvement and the number of reflux episodes as measured by pH impedance were similar for alginate compared with placebo.[39]

Pharmacologic visceral analgesics and other pharmacologic agents. Gamma-aminobutyric acid type B receptor agonists such as centrally acting baclofen or peripheral acting lesogaberan have been studied for their effect on gastroesophageal reflux and cough because of the wide distribution of gamma-aminobutyric acid type B receptors in the body including the airways and the lower esophageal sphincter. In a recent double-blind randomized placebo-controlled trial investigating the effects of lesogaberan in patients with refractory chronic cough, lesogaberan was shown to possibly reduce cough hypersensitivity, although the total number of coughs did not significantly decrease.[40] In another randomized controlled trial, cough sensitivity assessed using capsaicin challenge and patient report gastroesophageal reflux symptoms reduced after treatment with either gabapentin or baclofen in patients with suspected GER related to chronic cough.[41] However, because of the challenging side effect profile of baclofen, it is not routinely recommended as primary or adjunctive therapy in EER symptoms.

Pharmacologic visceral analgesia and cortical modulation through approaches such as neuromodulation or hypnotherapy may help reduce EER symptoms contributed by laryngeal hypersensitivity and hypervigilance. However, data on this topic are sparse and beyond the scope of this Clinical Practice Update.

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