# Diagnostic and Management Approach to Reflux-Related Cough

Ofer Z. Fass, MD, MS,[1] and Rena H. Yadlapati, MD, MS[2]

[1]Kenneth C. Griffin Esophageal Center of Northwestern Medicine, Department of Medicine, Division of Gastroenterology and Hepatology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

[2]Division of Gastroenterology, University of California San Diego, La Jolla, California

Corresponding author:
Ofer Z. Fass, MD, MS
Department of Medicine
Division of Gastroenterology and Hepatology
Feinberg School of Medicine
Northwestern University
211 East Ontario Street, Suite 1700
Chicago, IL 60611
Tel: (312) 926-4939
Fax: (312) 695-3999
E-mail: ofer.fass@northwestern.edu

**Abstract:** Chronic cough, defined as cough persisting longer than 8 weeks, affects approximately 10% of the global population and significantly impairs quality of life. Gastroesophageal reflux disease is a recognized cause of chronic cough, yet the relationship remains complex and poorly understood. Up to 75% of patients with reflux-related cough lack classic gastroesophageal symptoms such as heartburn or regurgitation, making diagnosis particularly challenging. Although direct tissue irritation by refluxate has been proposed as a primary mechanism, evidence also supports a vagally mediated esophageal-tracheobronchial reflex. Cough hypersensitivity is also recognized as an important mechanism, amplifying responses to reflux and contributing to persistent symptoms despite reflux-directed therapy. Diagnostic evaluation requires a structured approach integrating clinical assessment, empiric treatment trials, and objective testing including ambulatory reflux monitoring. Upper endoscopy may reveal reflux complications, but most patients with reflux-related cough have normal endoscopic findings. Management involves a stepwise approach beginning with lifestyle modifications and proton pump inhibitor therapy, with neuromodulators and behavioral interventions reserved for refractory cases. Surgical intervention may benefit carefully selected patients but requires shared decision-making regarding risks and benefits. Development of more accurate diagnostic tools and unified clinical guidelines will be critical for advancing the management of this difficult-to-treat condition. This article reviews reflux-related cough, including its diagnostic evaluation and management strategies.

**Keywords**
Chronic cough, gastroesophageal reflux disease, laryngopharyngeal reflux, ambulatory pH monitoring, proton pump inhibitors, neuromodulators

Chronic cough, defined as a cough persisting for more than 8 weeks, affects approximately 10% of the global population.[1,2] It significantly reduces quality of life and doubles direct medical costs compared with matched controls.[3] Gastroesophageal reflux disease (GERD) ranks among the most common causes of chronic cough; however, the proportion of chronic cough attributable to reflux varies considerably based on study populations and diagnostic criteria.[4] Although GERD affects 13% to 15% of the general population, chronic cough occurs in up to 14% of individuals with frequent heartburn.[5-7]

**Table 1.** Diagnostic Tools for Reflux-Related Cough

| Diagnostic tool | Purpose | Strengths | Limitations |
|---|---|---|---|
| Upper endoscopy | Identifies esophageal mucosal damage, wireless pH capsule placement | Can diagnose GERD per Lyon 2.0 criteria[46] | Often normal in NERD, poor sensitivity[15,46] |
| MII-pH monitoring | Quantifies reflux (acid/nonacid) over 24 hours, correlates with cough | Captures all reflux types and proximal extent,[13,35,49] high NPV[52,53] | Limited to 24 hours, lower yield with infrequent symptoms, low PPV[14,51] |
| Wireless pH monitoring | Quantifies acidic reflux over 96 hours, correlates with cough | Better for infrequent symptoms and day-to-day variability,[36,50] high NPV[52,53] | Acidic reflux only, no information on nonacidic reflux, low PPV[14,51] |
| PROs (RSI, RSS, HARQ) | Symptom screening | Easy to administer | Low specificity,[27,28,32] not diagnostic[9] |
| Acoustic monitoring | Temporal association of cough/reflux[18,59] | Real-time analysis, useful as an adjunct | No proven predictive value for treatment response |
| Inhaled capsaicin challenge | Objectively assesses cough reflex sensitivity[60,61] | Distinguishes between cough phenotypes (eg, refractory chronic cough, sensory hyperreactivity) | Overlap in test thresholds, lack of standardized protocols[103,104] |
| Laryngoscopy | Excludes other causes of LPS[9] | Identifies structural/malignant causes[54] | Nonspecific for reflux,[58] poor interobserver reliability[55-57] |

GERD, gastroesophageal reflux disease; HARQ, Hull Airway Reflux Questionnaire; LPS, laryngopharyngeal symptoms; MII-pH, multichannel intraluminal impedance and pH; NERD, nonerosive reflux disease; NPV, negative predictive value; PPV, positive predictive value; PROs, patient-reported outcomes; RSI, Reflux Symptom Index; RSS, Reflux Symptom Score.

Notably, up to 75% of patients with reflux-related cough lack classic gastroesophageal symptoms such as heartburn or regurgitation.[8]

Reflux-related cough falls within the broader spectrum of laryngopharyngeal reflux disease (LPRD), which encompasses other laryngopharyngeal symptoms (LPS) including hoarseness, throat clearing, excess phlegm, and throat pain.[9] However, the presence of LPS alone cannot confirm a reflux etiology, as these symptoms may result from various nonreflux conditions. This diagnostic challenge is particularly evident in chronic cough, where objective evidence of reflux is detected in only 2% to 41% of cases.[10] This wide range reflects heterogeneity in study design and variability in the criteria used to define a reflux-related cause. Cough hypersensitivity, characterized by an exaggerated cough reflex to diverse stimuli, may overlap with and amplify reflux-related cough, helping to explain why many patients continue to experience symptoms despite reflux-directed treatment.[11]

This article summarizes the current understanding of reflux-related cough, with a focus on pathophysiology, diagnostic evaluation, and management strategies.

## Pathophysiology

Cough hypersensitivity is a key mechanism that provides the framework for how reflux contributes to symptoms through two principal pathways: direct tissue irritation by refluxate and a vagally mediated esophageal-tracheobronchial reflex. Hypersensitivity reflects a state of neural sensitization in which even minimal reflux events, as well as unrelated stimuli (eg, strong odors, cold air, postnasal drainage, phonation), can trigger cough.[11] Supporting this concept, a prospective study using synchronized acoustic and impedance monitoring showed that both reflux and phonation events significantly increased the likelihood of subsequent cough episodes in patients with idiopathic chronic cough.[12] The risk was nearly 1.5-fold higher after reflux events alone and more than 1.7-fold higher when reflux and phonation occurred together, underscoring how reflux and airway hypersensitivity interact to perpetuate cough.

The direct irritation hypothesis receives support from multichannel intraluminal impedance and pH (MII-pH) studies showing that patients with positive symptom association between reflux and cough experience higher proportions of reflux events reaching the upper esophageal sphincter.[13] However, other MII-pH studies and pepsin assays demonstrate no significant differences in proximal reflux events or bronchoalveolar lavage pepsin levels between patients with chronic cough and healthy controls.[14] Moreover, inflammatory laryngeal findings in these patients often result from cough-related trauma rather than direct reflux injury.[15]

More consistent evidence supports a reflex-mediated mechanism. In double-blind studies, distal esophageal

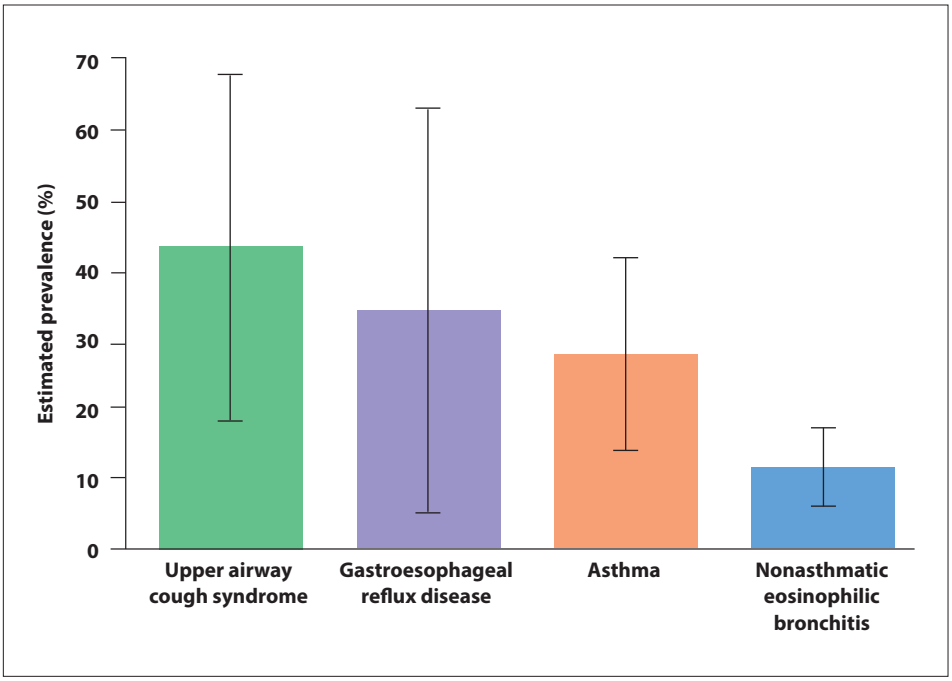


**Figure 1.** Estimated prevalence ranges of major chronic cough etiologies. Error bars represent the range of prevalence reported across published studies. Upper airway cough syndrome accounts for 18% to 67% of cases, gastroesophageal reflux disease for 5% to 62%, asthma for 14% to 41%, and nonasthmatic eosinophilic bronchitis for 6% to 17%.

acid infusion increased cough frequency and amplitude in patients with acidic reflux and chronic cough compared with saline infusion, an effect absent in healthy controls.[16] The response was attenuated by pretreatment with inhaled ipratropium or topical esophageal lidocaine. Similarly, intraesophageal acid infusion heightened cough sensitivity to inhaled capsaicin in GERD patients with chronic cough but not in those without cough.[17] In ambulatory reflux monitoring, approximately half of chronic cough patients show positive symptom association with acidic or weakly acidic reflux. These patients have increased cough reflex sensitivity but similar overall reflux exposure compared with those without symptom association, suggesting that central sensitization mechanisms likely underlie the reflux-cough association.[18] This study is notable for its rigorous methodology, using simultaneous ambulatory pH-impedance and acoustic cough monitoring in a well-characterized cohort to demonstrate consistent temporal associations between reflux events and cough while accounting for their bidirectional relationship. The study provides some of the strongest evidence supporting reflux as a trigger within the broader framework of cough hypersensitivity.

Esophageal dysmotility may also contribute to reflux-related cough by impairing acid clearance, increasing proximal reflux extent, and prolonging esophageal acid exposure.[19] Up to 67% of patients with chronic cough demonstrate abnormal esophageal manometry.[20-22] Studies incorporating ambulatory pH-impedance-pressure monitoring show these patients exhibit lower-amplitude esophageal contractions during primary peristalsis and synchronous (nonperistaltic) contractions during secondary peristalsis.[23]

The relationship between reflux and cough remains complex, as cough can result from diverse disease processes. Moreover, questions regarding cause and effect persist and hypersensitivity of both the esophagus and cough reflex can introduce variables that obscure the relationship.[15]

The San Diego Consensus recently provided a clinical framework for managing patients with LPS in response to diagnostic and therapeutic uncertainties surrounding LPRD.[9] This consensus introduced standardized terminology differentiating LPS, defined as laryngeal symptoms occurring at least twice weekly and persisting more than 8 weeks, from those attributable to objectively confirmed GERD (LPRD). Chronic cough is considered a type of LPS within this framework.

## Diagnosis

Diagnosing reflux-related cough presents inherent challenges owing to the high prevalence of asymptomatic reflux, symptom overlap with other common causes of chronic cough, and limitations in current diagnostic tools. A structured approach integrating clinical assessment, empiric treatment trials, endoscopic evaluation, and physiologic testing is often necessary to establish or exclude the diagnosis (Table 1).

### *History and Physical Examination*

Evaluation begins with a thorough history and physical examination to identify warning signs requiring urgent

attention. Alarm features warranting dedicated chest imaging and potential pulmonology referral include smoking history, hemoptysis, prominent dyspnea, substantial sputum production (>1 tablespoon/day), new-onset hoarseness, systemic symptoms (eg, night sweats, fevers, weight loss), and recurrent pneumonias.[24] Without alarm symptoms, other common nonreflux causes of chronic cough should be considered, including asthma, angiotensin-converting enzyme inhibitor use, obstructive sleep apnea, and upper airway cough syndrome (Figure 1). This differential is best addressed through collaboration with pulmonology and otolaryngology colleagues.

Regarding reflux-related cough, clinical history should assess both typical gastroesophageal reflux symptoms (eg, heartburn, regurgitation) and extraesophageal manifestations or LPS, as reflux-related cough may occur with or without classic esophageal symptoms.[25] The presence or absence of these symptoms helps determine eligibility for an empiric trial of antisecretory therapy and lifestyle measures to optimize gastroesophageal reflux physiology.[9]

### *Patient-Reported Outcome Measures*

Patient-reported outcome (PRO) measures demonstrate utility in evaluating symptom severity and treatment response in reflux but have limited diagnostic accuracy for reflux-related cough. The Reflux Symptom Index (RSI) is a widely used, 9-item, self-administered questionnaire assessing LPS severity, including cough.[26] Each symptom scores from 0 (no problem) to 5 (severe problem). However, MII-pH testing studies show that an RSI cutoff of at least 13 has low specificity (32%) for detecting proximal or pharyngeal reflux.[27] Subsequent studies have replicated these findings.[28]

The Reflux Symptom Score (RSS) builds upon the RSI by assessing both frequency and severity across a broader symptom range.[29] Compared with the RSI, the RSS demonstrates higher sensitivity (92.8% vs 48.2%) and stronger concordance with objective testing such as hypopharyngeal-esophageal MII-pH monitoring ($\kappa$ = 0.66 vs 0.21).[30] However, the RSS is validated for LPRD generally, not specifically for reflux-related cough, and according to the San Diego Consensus, does not meet thresholds for a definitive diagnostic tool.[9]

The Hull Airway Reflux Questionnaire (HARQ) is a 14-item tool developed to identify airway reflux symptoms, particularly in patients with chronic cough.[31] Like the RSI and RSS, it scores items from 0 to 5 but focuses specifically on airway symptoms. Although more sensitive in identifying a reflux-related phenotype in chronic cough, it lacks specificity for LPRD and cannot substitute for objective testing.[32]

Other cough-specific instruments, such as the Leicester Cough Questionnaire and Cough Severity Index, primarily assess quality of life and symptom burden.[32-34] These tools are not specific to reflux and cannot distinguish reflux-related cough from other etiologies.

Accordingly, the San Diego Consensus recommends against using PROs, including the RSI, RSS, and HARQ, as stand-alone diagnostic tools for LPRD or reflux-related cough owing to insufficient specificity.[9] Nonetheless, elevated scores may support decisions to pursue further diagnostic testing.

### *Empiric Medical Treatment*

The decision to initiate empiric treatment for reflux-related cough is guided primarily by the presence or absence of typical gastroesophageal reflux symptoms such as heartburn or regurgitation. In patients with these symptoms, GERD pretest probability is high, with reported prevalence rates of 60% to 70%.[35] In contrast, among individuals presenting solely with LPS (including cough), objective evidence of GERD is found in approximately 35%.[36] Given these pretest probability differences, empiric reflux therapy is recommended only for patients with chronic cough who also report typical reflux symptoms.[9,15]

Empiric therapy typically consists of standard-dose proton pump inhibitor (PPI) therapy (eg, omeprazole 20 mg) taken twice daily for at least 3 months. As with standard therapy, symptomatic response of reflux-induced cough may require up to 3 months, with full resolution sometimes requiring 5 to 6 months of treatment.[10,37,38] Shorter duration may be insufficient to capture therapeutic benefit and could lead to premature discontinuation.

Adjunctive lifestyle modifications aim to reduce reflux burden and include avoidance of trigger foods, head-of-bed elevation, tobacco cessation, avoiding tight-fitting clothing, ensuring a time gap between meals and recumbency, and interventions aimed at weight loss in overweight or obese individuals.[35] These changes can augment antireflux therapy and improve symptoms and treatment outcomes in patients with LPS, including those with cough.[15,39-42] Alginate therapy, administered 4 times daily (after meals and at bedtime), can be incorporated into empiric treatment, as it improves GERD symptoms,[43] augments PPI efficacy,[44] and reduces LPS severity.[45]

Patients experiencing improvement in both typical reflux symptoms and chronic cough following empiric PPI treatment likely have reflux-related cough. These individuals may continue therapy, with the goal of tapering PPIs to the lowest effective dose. Objective esophageal testing may still be appropriate in selected cases, particularly when long-term PPI therapy is anticipated or prior to consideration of invasive antireflux procedures.[9] Failure to achieve symptom resolution with empiric therapy does not exclude underlying reflux and should prompt further diagnostic evaluation.

### *Endoscopy*

Objective testing for reflux is indicated in patients with chronic cough who lack typical reflux symptoms, in patients with both cough and reflux symptoms who fail to respond to empiric medical therapy, and in patients who improve with empiric therapy but are being considered for long-term treatment or invasive antireflux interventions.[9] As an initial diagnostic step, upper endoscopy is often performed in patients with concomitant reflux symptoms to assess for reflux-related complications such as erosive esophagitis, Barrett esophagus, or peptic strictures.[35] According to the Lyon Consensus 2.0, endoscopic evidence of Los Angeles grade B to D esophagitis or biopsy-proven Barrett esophagus sufficiently establishes GERD diagnosis.[46]

The role of endoscopy in patients without typical reflux symptoms is less clear. Its diagnostic yield is limited by low sensitivity for nonerosive reflux disease, as most individuals with reflux-related cough have normal-appearing esophagus on endoscopic evaluation.[15,46] However, the presence of hiatal hernia or a disrupted antireflux barrier may support GERD diagnosis. Notably, a recent study found that up to 47% of patients presenting with LPS had erosive esophagitis and/or hiatal hernia.[47]

### *Ambulatory Reflux Testing*

If endoscopy is unrevealing or not indicated, the next evaluation step is ambulatory reflux monitoring. The primary role of ambulatory reflux testing is to quantify esophageal acid exposure to establish GERD diagnosis and assess temporal correlation between reflux events and symptoms, including cough, using symptom association.[30,48]

MII-pH monitoring offers the advantage of detecting not only acidic reflux but also weakly acidic and nonacidic reflux, which have been implicated in chronic cough.[13] It also provides information on reflux proximal extent, which may be relevant in this population.[49] In contrast, wireless pH monitoring allows extended recording over 48 to 96 hours, increasing diagnostic yield by capturing day-to-day variability and infrequent symptoms, and can be placed during endoscopy.[50] Both tests should be performed off acid suppression if GERD is unproven.

A distal esophageal acid exposure time (AET) greater than 6% is diagnostic of GERD, whereas an AET less than 4% (or less than 4% on all recording days for wireless monitoring) essentially rules out GERD.[46] Day-to-day variability in acid exposure can confound reflux testing; therefore, 96-hour wireless pH monitoring has become the preferred modality for detecting pathologic GERD in patients with LPS. In a recent multicenter study of patients with LPS, GERD diagnostic yield was 50% with prolonged wireless pH monitoring compared with 27% with 24-hour MII-pH testing.[36] In patients with confirmed GERD and persistent cough despite adequate PPI therapy, on-treatment MII-pH testing may be considered to evaluate for ongoing acidic or nonacidic reflux as a potential symptom trigger.[35]

Although reflux testing is essential for diagnosing or excluding pathologic acid exposure, its correlation with chronic cough remains unclear. Positive reflux testing does not reliably predict cough response to antireflux therapy and has shown limited positive predictive value.[14,51] In contrast, when reflux testing rules out GERD, the negative predictive value for cough response approaches 100%, indicating that antireflux therapy is unlikely to be beneficial.[52,53] Thus, a positive test does not confirm reflux as the cause of cough or predict treatment response, but a negative test strongly suggests that reflux is not the underlying etiology.

### *Laryngoscopy*

In the broader evaluation of LPS, laryngoscopy is recommended to exclude alternative etiologies such as malignancy or vocal cord dysfunction.[9,54] Findings commonly attributed to reflux, such as posterior commissure hypertrophy, laryngeal erythema, and vocal cord edema, are highly nonspecific, frequently observed in asymptomatic individuals (up to 93%), and demonstrate poor interobserver reliability.[55-57] Moreover, laryngeal irritation in these patients often results from cough-related trauma rather than direct reflux injury.[15] Laryngoscopic scoring systems, such as the Reflux Finding Score, show poor correlation with objective reflux testing and do not reliably differentiate reflux-related cough from other causes.[58] Although laryngoscopy may help identify nonreflux causes of laryngeal symptoms, it cannot confirm reflux as the etiology of cough.

### *Other Diagnostics*

Several additional modalities have been explored for diagnosing reflux-related cough and GERD. Acoustic monitoring combined with 24-hour MII-pH testing has been used to improve detection of temporal relationships between reflux events and cough. In a study of 72 patients with chronic cough, acoustic monitoring identified a positive reflux-cough association in nearly half of participants.[18] More recently, a study using a lung sound–monitoring device during MII-pH testing assessed nocturnal respiratory symptoms and similarly found that approximately 50% of patients with reflux experienced temporally associated cough.[59] However, neither study evaluated whether this association predicted response to antireflux therapy.

Given the role of cough hypersensitivity in symptom generation, inhaled capsaicin challenge provides an

**Table 2.** Treatment Options for Reflux-Related Cough

| Treatment | Mechanism | Evidence |
|---|---|---|
| Lifestyle modifications | Reduce reflux triggers and burden (eg, weight loss, diet, head-of-bed elevation) | Weight loss improves cough severity[67,68]; antireflux diet helps in mild cases[70] |
| PPIs | Acid suppression | Mixed efficacy, benefit mostly in confirmed GERD,[59,73] delayed response (3-6 months)[37,38] |
| Alginates | Mechanical barrier and acid neutralization | Improve symptoms when added to PPIs,[44] not superior to placebo as monotherapy[79] |
| Neuromodulators | Reduce cough reflex sensitivity, treat hypervigilance/laryngeal hypersensitivity | Gabapentin reduces cough frequency (NNT=3.5)[81]; amitriptyline > codeine with guaifenesin for cough[84] |
| GABA-B agonists | Reduce transient LES relaxations and cough sensitivity | Baclofen reduces reflux and cough[85] |
| Purinergic receptor antagonists | Reduce C-fiber activation, thereby inhibiting cough[88] | Modest improvement in cough frequency and severity over placebo[87] |
| Prokinetics | Enhance motility and acid clearance | Some benefit when added to PPIs,[89] mixed results on symptom and laryngoscopy scores[90] |
| Antireflux surgery | Mechanical control of reflux (both acidic and nonacidic) | Symptom improvement in selected patients with proven reflux and typical symptoms[51,92] |
| Transoral incisionless fundoplication | Endoscopically recreates antireflux barrier | RSI improvement, reduced AET, and PPI cessation in LPS patients[95] |
| Laryngeal recalibration therapy | Suppresses laryngeal hypersensitivity and abnormal reflexes | Improves cough in chronic LPS[101] independent of GERD status[100] |
| Cognitive behavioral therapy | Addresses anxiety, hypervigilance, maladaptive cough behaviors | Addresses hypervigilance/anxiety cycle in chronic cough and other disorders of brain-larynx interaction[102] |

AET, acid exposure time; GABA-B, gamma-aminobutyric acid type B; GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; LPS, laryngopharyngeal symptoms; NNT, number needed to treat; PPI, proton pump inhibitor; RSI, Reflux Symptom Index.

objective measure of cough reflex sensitivity. Patients with chronic cough, including reflux-related cough, exhibit heightened responses with lower capsaicin thresholds than healthy controls.[18,60,61] Although useful in research and specialized diagnostic settings to confirm abnormal reflex sensitivity and distinguish phenotypes such as refractory chronic cough or sensory hyperreactivity, capsaicin challenge is not routinely used in standard clinical practice.

Pepsin and oropharyngeal pH monitoring have been investigated as tools to assess extraesophageal reflux, although they represent fundamentally different approaches. Oropharyngeal pH monitoring measures proximal acid exposure but is no longer considered a reliable diagnostic tool owing to poor correlation with established reflux testing and substantial overlap between symptomatic individuals and healthy controls.[62-64] In contrast, salivary pepsin testing, which assesses pepsin as a biomarker of refluxate, remains under investigation. Although some studies suggest its potential utility in patients with laryngeal or respiratory symptoms, other studies highlight variability in sensitivity and specificity.[65,66]

Similar to conventional reflux monitoring, positive symptom-reflux associations identified through these emerging diagnostic tools do not reliably predict therapeutic benefit from antireflux treatment.[14,51]

## Management

Management of reflux-related cough remains challenging owing to heterogeneity of symptom presentation, overlap with other etiologies of chronic cough, and inconsistent correlation between diagnostic test results and treatment response. For patients with confirmed reflux-related cough, a stepwise approach beginning with medical and lifestyle interventions is recommended, whereas patients with refractory symptoms or diagnostic uncertainty may require escalation to advanced testing or procedural interventions (Table 2, Figure 2).

### *Lifestyle Interventions*

Lifestyle measures, as previously described, aim to reduce reflux burden and improve PPI effectiveness. Although evidence supporting these interventions for cough specifically is mixed, they are generally low cost, low risk, and simple to implement, making them commonly recommended.

Multiple studies demonstrate benefits of weight reduction for reflux-related cough. A randomized controlled

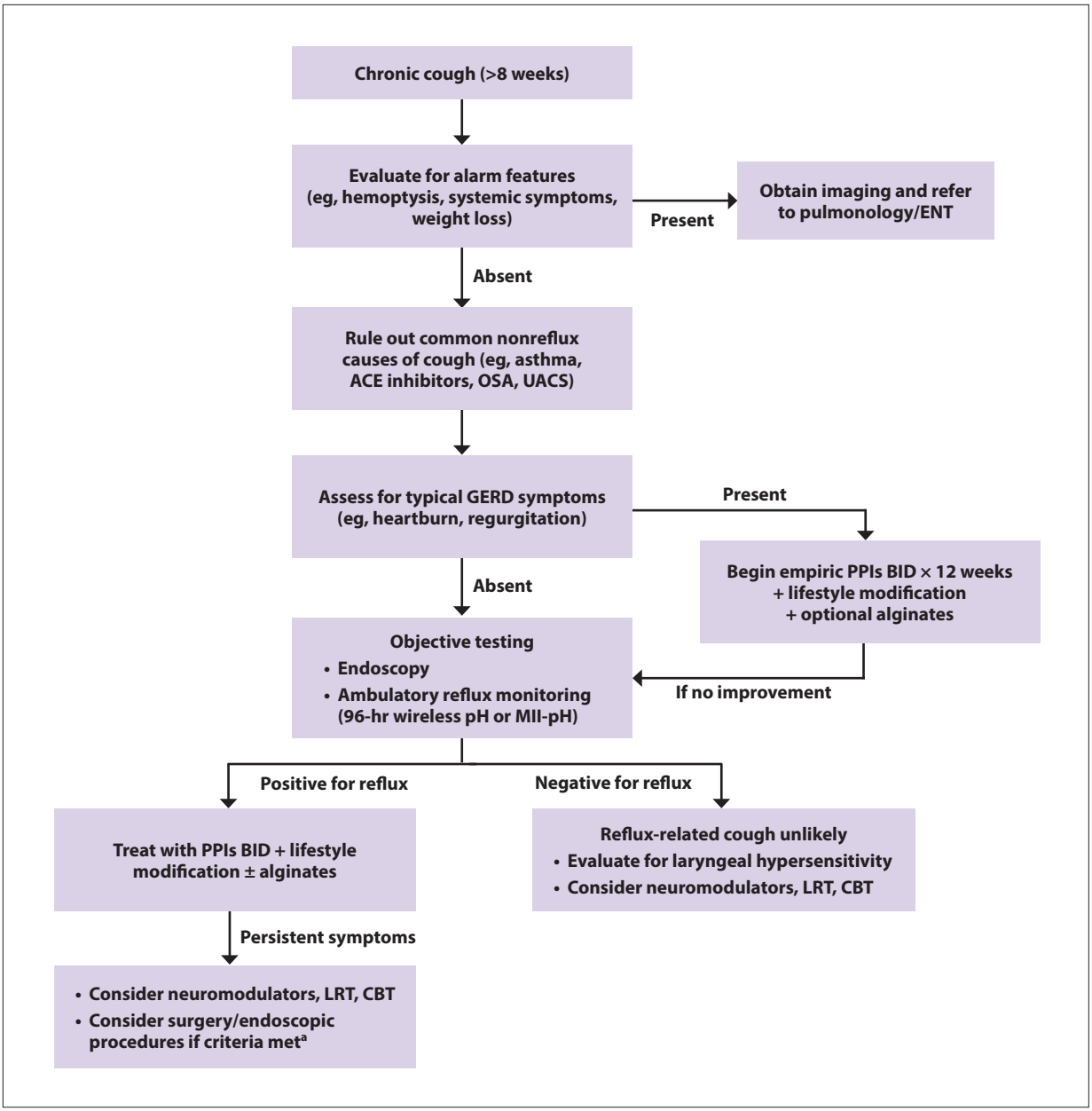


**Figure 2.** Management algorithm for reflux-related cough.

[a]Presence of typical heartburn symptoms, prior response to PPIs, ongoing reflux despite therapy, and high acid burden on ambulatory reflux testing.

ACE, angiotensin-converting enzyme; BID, two times a day; CBT, cognitive behavioral therapy; ENT, ear nose throat/otolaryngology; GERD, gastroesophageal reflux disease; LRT, laryngeal recalibration therapy; MII-pH, multichannel intraluminal impedance and pH; OSA, obstructive sleep apnea; PPI, proton pump inhibitor; UACS, upper airway cough syndrome.

trial comparing dietary modification to cisapride found that cough severity improvement correlated with weight loss regardless of treatment group, with notable benefits in patients losing more than 5 pounds.[67] Similarly, a trial of 20 overweight patients showed that weight loss reduced cough symptoms regardless of dietary assignment, whereas high-calorie, high-fat diets increased cough scores.[68]

Evidence also supports broader lifestyle modifications. A double-blind trial of 42 patients with LPS found that compliance with lifestyle measures was significantly associated with greater symptom improvement despite no difference between rabeprazole and placebo groups.[69] However, this study lacked objective GERD confirmation.

More recently, an observational study of 80 patients with MII-pH–confirmed GERD demonstrated that antireflux diet alone improved symptoms in 83% of

patients with mild cough, comparable with combination therapy with PPIs, alginates, and dietary modification in severe cases.[70]

In summary, lifestyle interventions can be broadly recommended for patients with suspected reflux-related cough. Among these, the strongest evidence supports weight loss in overweight or obese individuals and avoidance of refluxogenic foods.

### *Proton Pump Inhibitors*

Pharmacologic management addresses both reflux burden and cough hypersensitivity. PPIs remain the primary treatment for acid suppression, although their efficacy in this population is debated. A Cochrane review found no significant difference between PPIs and placebo in achieving cough resolution or improvement.[71] Similarly, an older meta-analysis evaluating PPI response in reflux-related cough reported no clear benefit over placebo.[72] However, both reviews included studies lacking objective evidence of GERD, such as abnormal endoscopy or ambulatory pH testing, limiting applicability to reflux-related cough.

Closer examination of subgroup analyses indicates that patients with objectively documented pathologic reflux, such as abnormal esophageal acid exposure or positive symptom association on MII-pH monitoring, derive greater benefit from PPI therapy.[10] Reported response rates range from 12.5% to 35.8% in patients with confirmed reflux, compared with 0% to 8.6% in those without.[73,74] This observation supports the rationale for PPI trials in chronic cough, provided that careful patient selection and follow-up assessment are performed. Up-front physiologic testing, including MII-pH monitoring and assessment of parameters such as mean nocturnal baseline impedance and postreflux swallow-induced peristaltic wave index, may further improve identification of PPI responders.[74]

Despite mixed efficacy data, PPIs are still recommended for treating reflux-related cough based on their effectiveness in GERD.[9,75] To optimize benefit, they should be combined with lifestyle modifications and alginate therapy.[9,15] When used, PPIs should be given twice daily. A prospective cohort study in patients with LPS (including cough) showed a higher symptom response rate with twice-daily PPI therapy (50%) vs once-daily dosing (28%).[76] Among nonresponders to once-daily therapy, 54% improved after escalation to twice-daily dosing. Symptom improvement may take up to 3 months, with some patients requiring 5 to 6 months for full resolution.[37,38]

Several mechanisms may account for persistent cough despite PPI therapy. Nonacidic reflux, which is not suppressed by PPIs, can still trigger cough via a vagally mediated esophageal-tracheobronchial reflex. Another important consideration is coexistence of disorders of brain-larynx interaction, such as laryngeal hyperresponsiveness and hypervigilance, which may contribute to persistent symptoms despite adequate reflux control.[9] Ambulatory reflux testing performed while on treatment can determine whether persistent cough is caused by ongoing acidic reflux, nonacidic reflux, or if no reflux-cough association exists. The latter would support a nonreflux mechanism such as cough hypersensitivity, in which case, behavioral therapy or neuromodulators may be appropriate.

### *Alginates*

Alginates are polysaccharide derivatives of seaweed that polymerize in the presence of gastric acid to form a gel-like matrix. This matrix neutralizes the postprandial acid pocket and acts as a mechanical barrier, reducing esophageal acid exposure and limiting the proximal extent of reflux.[77] In vitro studies show that alginates better preserve epithelial barrier integrity in esophageal and vocal cord epithelial cells during pepsin-acid insult compared with saline, supporting their protective mechanism.[78]

Randomized trials show that adding alginates (administered 4 times daily) to once-daily PPI therapy leads to greater symptom improvement than PPI therapy alone, supporting their role as adjunctive treatment.[44] However, the efficacy of alginates alone is less certain. In a double-blind, placebo-controlled trial in adults with LPS, alginate therapy did not demonstrate superiority over placebo for symptom improvement or reduction in reflux episodes as measured by pH impedance, highlighting a substantial placebo effect and the importance of lifestyle modification.[79]

A recent prospective observational study in adults with objectively confirmed LPS found that combination therapy with antireflux diet, PPIs, and alginates was effective for severe chronic cough, but the study design did not isolate the effect of alginates alone. In patients with mild cough, antireflux diet alone yielded comparable symptom improvement.[70]

In contrast, an open-label trial in patients with LPS and abnormal laryngoscopy reported significant symptom improvement and better laryngoscopic findings at 6 months in those treated with alginates compared with no treatment, although the lack of placebo control limits interpretation.[45] These findings support the concept of mucosal barrier protection as a therapeutic approach in reflux-related cough.

Given their favorable safety profile and evidence of PPI augmentation, alginates are generally recommended as adjunctive therapy for reflux-related cough. When used, they should be taken 4 times daily, after meals and at bedtime.[9]

### *Neuromodulators*

In patients with persistent cough despite reflux-targeted therapy, coexisting disorders of brain-larynx interaction (laryngeal hypersensitivity or hypervigilance) and nonacidic reflux eliciting the esophageal-tracheobronchial reflex should be considered. In these settings, neuromodulators may help by reducing cough reflex sensitivity and dampening reflux-triggered reflexes.

Gabapentin is among the most studied agents for chronic cough. It is typically initiated at 100 to 300 mg once or twice daily and titrated to effect, up to a maximum of 1800 mg/day in divided doses.[80] Randomized trials show efficacy, with one reporting significant cough improvement over 8 weeks and a number needed to treat of 3.5.[81] Pregabalin has shown similar benefit in an observational study of 12 patients, with symptom improvement reported after 1 month.[82] Dosing typically begins at 25 to 75 mg twice daily and may be titrated up to 150 mg twice daily over 4 weeks.[80] Both agents can cause somnolence and should be titrated slowly to the lowest effective dose.

Tricyclic antidepressants have demonstrated benefit in reflux-related cough, mirroring their effectiveness in treating visceral and esophageal hypersensitivity.[83] Amitriptyline has been specifically studied for cough and shown superiority to codeine/guaifenesin in a randomized trial.[84] It is typically initiated at 10 mg nightly and titrated as needed up to 100 mg, although use may be limited by anticholinergic side effects and sedation.[80]

Gamma-aminobutyric acid type B (GABA-B) receptor agonists have also been studied owing to the presence of GABA-B receptors in the respiratory tract and lower esophageal sphincter.[48] Baclofen, a centrally acting GABA-B agonist, has been shown to reduce reflux and cough sensitivity, with efficacy similar to gabapentin, but its use is often limited by central nervous system side effects.[85]

Gefapixant is a purinergic receptor antagonist targeting P2X3 receptors that has been evaluated in patients with chronic cough.[86,87] P2X3 is an ion channel expressed on airway C fibers that, when blocked, reduces C-fiber activation and inhibits cough.[88] Clinical trials suggest that gefapixant may decrease cough frequency and severity, although improvements over placebo were modest and treatment was limited by taste disturbances.[87] Gefapixant is currently approved in Europe and Japan, but it has not yet been approved in the United States, in part owing to concerns regarding placebo effects and the magnitude of clinical benefit.

### *Prokinetics*

Prokinetic agents have been evaluated for their ability to reduce nonacidic reflux but have shown limited and inconsistent benefit. In a prospective randomized trial of patients with LPS, once-daily PPI, twice-daily PPI, and twice-daily PPI plus mosapride therapy produced similar symptom improvement. However, the addition of mosapride improved laryngoscopic findings and appeared more beneficial in overweight and obese patients.[89] A systematic review identified only 4 studies assessing prokinetics for LPS; 3 showed symptom improvement, but none demonstrated significant changes in laryngoscopic appearance.[90] Given limited evidence and mixed outcomes, prokinetics are not recommended for treating reflux-related cough.

### *Endoscopic and Surgical Interventions*

The role of endoscopic and surgical interventions in reflux-related cough remains uncertain. Smaller studies suggest that antireflux surgery may benefit selected patients with LPS. In a retrospective study of 29 patients undergoing Nissen fundoplication, 86% experienced near-complete symptom resolution without the need for PPIs.[91]

Another study of 18 patients with medically refractory extraesophageal symptoms and positive MII-pH testing found that 33% reported complete symptom resolution after antireflux surgery, 39% reported improvement, and 28% noted no change.[51] Although pH testing metrics did not predict response, the presence of heartburn or regurgitation at baseline was associated with better outcomes.

More recently, a retrospective review of 128 patients who underwent magnetic sphincter augmentation for LPS reported symptom improvement in 80.4% of patients.[92] Predictors of success included typical heartburn symptoms prior to surgery and normal esophageal body motility. However, the number of proximal acid exposure events was similar between responders and nonresponders.

Systematic reviews have attempted to clarify the role of surgery in reflux-related cough and LPS. One review of 27 observational studies on surgical treatment for extraesophageal GERD manifestations found that heterogeneity in diagnostic methods and surgical techniques limited conclusions.[93] The authors noted a lack of randomized trials comparing surgery with medical therapy and concluded that surgery may benefit a subset of patients with nonacidic reflux when carefully selected. A second systematic review of 34 observational studies reported similar limitations owing to study design variability.[94]

Transoral incisionless fundoplication (TIF) is the only endoscopic procedure specifically evaluated in LPS, including reflux-related cough. In a study of 49 patients with objective evidence of GERD, 85% had normalization of their RSI scores, 75% had normalization of AET at 6 months, and 80% remained off PPIs at 12 months after TIF.[95] Longer-term randomized data suggest more modest effects. In the TEMPO study, 88% of patients reported resolution of atypical symptoms and 71% discontinued PPIs at 3 years, although normalization of pH scores was not consistently achieved.[96] At 5 years, 34% of

patients had resumed PPI therapy.[97] The RESPECT randomized, sham-controlled trial showed similar reductions in symptom scores between TIF and sham groups, and although objective pH parameters improved after TIF, complete normalization remained uncommon.[98]

The available evidence has led professional societies to recommend that antireflux surgery or endoscopic procedures be reserved for carefully selected patients. Appropriate candidates include those with typical reflux symptoms, prior response to PPIs, ongoing reflux despite therapy, and high acid burden on ambulatory reflux testing. Referral should involve shared decision-making that clearly outlines potential risks, benefits, and alternatives.[48]

### *Behavioral Interventions*

Patients who do not respond to antireflux therapy should be evaluated for coexisting disorders of brain-larynx interaction, such as laryngeal hypersensitivity or hypervigilance. These conditions are characterized by heightened laryngeal sensitivity to physiologic stimuli, leading to hyperresponsiveness that manifests as coughing, tension, and abnormal breathing patterns. Coughing may then contribute to anxiety and hypervigilance, which further amplify hypersensitivity.[9]

As an adjunct or alternative to neuromodulators, behavioral therapies such as laryngeal recalibration therapy (LRT) and cognitive behavioral therapy (CBT) may help break this cycle. Patients with reflux-related cough who may benefit from such interventions can be identified using the Laryngeal Cognitive Affective Tool, with abnormal scores defined as at least 33.[99]

LRT, typically delivered by a speech-language pathologist, targets maladaptive laryngeal sensory-motor patterns through mechanical desensitization and cognitive strategies. Its goal is to reduce cough frequency and severity by suppressing exaggerated laryngeal reflexes. Recent prospective data support the role of LRT in patients with chronic LPS, with most reporting symptom improvement regardless of confirmed GERD.[100] This is consistent with evidence from randomized controlled trials showing that speech pathology and physiotherapy-based interventions improve cough-related quality of life and reduce cough frequency in patients with refractory chronic cough.[101] These interventions often include education, cough suppression techniques, laryngeal hygiene, breathing exercises, and psychoeducational counseling.

CBT may also play a supportive role, particularly in patients with comorbid anxiety or depression. Although not a direct treatment for cough, its efficacy in disorders of gut-brain interaction suggests potential utility in related maladaptive cognitive processes involved in brain-larynx interaction.[102]

CBT and LRT are evidence-based, nonpharmacologic options that can complement medical therapy for chronic cough, especially in cases associated with laryngeal hypersensitivity or hypervigilance. These therapies are best delivered as part of a multidisciplinary approach that also addresses reflux, dietary factors, and neuromodulation.

## Conclusion

Reflux-related cough represents a complex diagnostic and therapeutic challenge in clinical practice. A systematic, stepwise approach incorporating comprehensive symptom assessment, empiric therapy trials, and objective physiologic testing can effectively identify appropriate candidates for treatment. Management strategies are multifaceted and typically encompass lifestyle modifications, including dietary interventions, pharmacologic antireflux therapy, and, in carefully selected patients with refractory disease, surgical intervention. Disorders of brain-larynx interaction may overlap with reflux-related cough and should be considered as a potential mechanism underlying PPI treatment failure. In such cases, behavioral interventions and neuromodulatory therapies play a crucial role in reducing laryngeal hypersensitivity and hypervigilance. Enhanced diagnostic precision and standardized treatment algorithms are needed to facilitate more effective management of this clinically burdensome condition.

### *Disclosures*

*Dr Fass has no relevant conflicts of interest to disclose. Dr Yadlapati has served as a consultant for Phathom Pharmaceuticals, StatLink MD, Braintree Pharmaceuticals, Reckitt Benckiser Healthcare Ltd, and Medtronic and has served on the advisory board for RJS Mediagnostix.*

### *Funding*

*Dr Yadlapati is supported by NIH K23 DK125266 (as principal investigator) and NIH R01 DK139089.*

## References

1. Song WJ, Chang YS, Faruqi S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J*. 2015;45(5):1479-1481.
2. Irwin RS, French CL, Chang AB, Altman KW; CHEST Expert Cough Panel. Classification of cough as a symptom in adults and management algorithms: CHEST Guideline and Expert Panel Report. *Chest*. 2018;153(1):196-209.
3. Chodick G, Barer Y, Blay Hagai T, et al. Epidemiology and healthcare service utilization among adults with chronic cough. *J Clin Med*. 2024;13(11):3230.
4. Kastelik JA, Aziz I, Ojoo JC, Thompson RH, Redington AE, Morice AH. Investigation and management of chronic cough using a probability-based algorithm. *Eur Respir J*. 2005;25(2):235-243.
5. Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*. 1997;112(5):1448-1456.
6. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. *Gut*. 2018;67(3):430-440.
7. Hallan A, Bomme M, Hveem K, Møller-Hansen J, Ness-Jensen E. Risk factors on the development of new-onset gastroesophageal reflux symptoms. A population-based prospective cohort study: the HUNT study. *Am J Gastroenterol*. 2015;110(3):393-400; quiz 401.
8. Irwin RS, French CL, Curley FJ, Zawacki JK, Bennett FM. Chronic cough due

to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. *Chest*. 1993;104(5):1511-1517.
9. Yadlapati R, Weissbrod P, Walsh E, et al. The San Diego Consensus for laryngopharyngeal symptoms and laryngopharyngeal reflux disease [published online April 8, 2025]. *Am J Gastroenterol*. doi:10.14309/ajg.0000000000003482.
10. Kahrilas PJ, Howden CW, Hughes N, Molloy-Bland M. Response of chronic cough to acid-suppressive therapy in patients with gastroesophageal reflux disease. *Chest*. 2013;143(3):605-612.
11. Chung KF, McGarvey L, Song WJ, et al. Cough hypersensitivity and chronic cough. *Nat Rev Dis Primers*. 2022;8(1):45.
12. Francis DO, Slaughter JC, Ates F, et al. Airway hypersensitivity, reflux, and phonation contribute to chronic cough. *Clin Gastroenterol Hepatol*. 2016;14(3):378-384.
13. Patterson N, Mainie I, Rafferty G, et al. Nonacid reflux episodes reaching the pharynx are important factors associated with cough. *J Clin Gastroenterol*. 2009;43(5):414-419.
14. Decalmer S, Stovold R, Houghton LA, et al. Chronic cough: relationship between microaspiration, gastroesophageal reflux, and cough frequency. *Chest*. 2012;142(4):958-964.
15. Kahrilas PJ, Altman KW, Chang AB, et al; CHEST Expert Cough Panel. Chronic cough due to gastroesophageal reflux in adults: CHEST Guideline and Expert Panel Report. *Chest*. 2016;150(6):1341-1360.
16. Ing AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. *Am J Respir Crit Care Med*. 1994;149(1):160-167.
17. Javorkova N, Varechova S, Pecova R, et al. Acidification of the oesophagus acutely increases the cough sensitivity in patients with gastro-oesophageal reflux and chronic cough. *Neurogastroenterol Motil*. 2008;20(2):119-124.
18. Smith JA, Decalmer S, Kelsall A, et al. Acoustic cough-reflux associations in chronic cough: potential triggers and mechanisms. *Gastroenterology*. 2010;139(3):754-762.
19. Herregods TVK, Pauwels A, Jafari J, et al. Determinants of reflux-induced chronic cough. *Gut*. 2017;66(12):2057-2062.
20. Knight RE, Wells JR, Parrish RS. Esophageal dysmotility as an important co-factor in extraesophageal manifestations of gastroesophageal reflux. *Laryngoscope*. 2000;110(9):1462-1466.
21. Sykes DL, Crooks MG, Hart SP, Jackson W, Gallagher J, Morice AH. Investigating the diagnostic utility of high-resolution oesophageal manometry in patients with refractory respiratory symptoms. *Respir Med*. 2022;202:106985.
22. Kastelik JA, Redington AE, Aziz I, et al. Abnormal oesophageal motility in patients with chronic cough. *Thorax*. 2003;58(8):699-702.
23. Li X, Lin S, Wang Z, et al. Gastroesophageal reflux disease and chronic cough: a possible mechanism elucidated by ambulatory pH-impedance-pressure monitoring. *Neurogastroenterol Motil*. 2019;31(12):e13707.
24. Gibson PG, Vertigan AE. Management of chronic refractory cough. *BMJ*. 2015;351:h5590.
25. Connor NP, Palazzi-Churas KLP, Cohen SB, Leverson GE, Bless DM. Symptoms of extraesophageal reflux in a community-dwelling sample. *J Voice*. 2007;21(2):189-202.
26. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice*. 2002;16(2):274-277.
27. DeVore EK, Chan WW, Shin JJ, Carroll TL. Does the reflux symptom index predict increased pharyngeal events on HEMII-pH testing and correlate with general quality of life? *J Voice*. 2021;35(4):625-632.
28. Geeratragool T, Maneerattanaporn M, Prapruetkit J, Chuenprapai P, Chongkolwatana C, Leelakusolvong S. Association between laryngopharyngeal reflux clinical scores and esophageal multichannel intraluminal impedance pH monitoring interpretation according to Lyon Consensus 2.0. *Dis Esophagus*. 2025;38(1):doae098.
29. Lechien JR, Bobin F, Muls V, et al. Validity and reliability of the reflux symptom score. *Laryngoscope*. 2020;130(3):E98-E107.
30. Zhang C, Liu Z, Zhang J, et al. Comparison of reflux symptom score versus reflux symptom index in screening laryngopharyngeal reflux. *Laryngoscope*. 2023;133(9):2104-2109.
31. Morice AH, Faruqi S, Wright CE, Thompson R, Bland JM. Cough hypersensitivity syndrome: a distinct clinical entity. *Lung*. 2011;189(1):73-79.
32. Zhang M, Sykes DL, Brindle K, Sadofsky LR, Morice AH. Chronic cough—the limitation and advances in assessment techniques. *J Thorac Dis*. 2022;14(12):5097-5119.
33. Shembel AC, Rosen CA, Zullo TG, Gartner-Schmidt JL. Development and validation of the cough severity index: a severity index for chronic cough related to the upper airway. *Laryngoscope*. 2013;123(8):1931-1936.
34. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MDL, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax*. 2003;58(4):339-343.
35. Fass R. Gastroesophageal reflux disease. *N Engl J Med*. 2022;387(13):1207-1216.
36. Krause AJ, Greytak M, Kaizer AM, et al. Diagnostic yield of ambulatory reflux monitoring systems for evaluation of chronic laryngeal symptoms. *Am J Gastroenterol*. 2024;119(4):627-634.
37. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis*. 1990;141(3):640-647.
38. Irwin RS, Zawacki JK, Curley FJ, French CL, Hoffman PJ. Chronic cough as the sole presenting manifestation of gastroesophageal reflux. *Am Rev Respir Dis*. 1989;140(5):1294-1300.
39. Yang J, Dehom S, Sanders S, Murry T, Krishna P, Crawley BK. Treating laryngopharyngeal reflux: evaluation of an anti-reflux program with comparison to medications. *Am J Otolaryngol*. 2018;39(1):50-55.
40. Khan BA, Sodhi JS, Zargar SA, et al. Effect of bed head elevation during sleep in symptomatic patients of nocturnal gastroesophageal reflux. *J Gastroenterol Hepatol*. 2012;27(6):1078-1082.
41. Chappity P, Kumar R, Deka RC, Chokkalingam V, Saraya A, Sikka K. Proton pump inhibitors versus solitary lifestyle modification in management of laryngopharyngeal reflux and evaluating who is at risk: scenario in a developing country. *Clin Med Insights Ear Nose Throat*. 2014;7:1-5.
42. Lechien JR, Huet K, Khalife M, et al. Alkaline, protein, low-fat and low-acid diet in laryngopharyngeal reflux disease: our experience on 65 patients. *Clin Otolaryngol*. 2019;44(3):379-384.
43. Leiman DA, Riff BP, Morgan S, et al. Alginate therapy is effective treatment for gastroesophageal reflux disease symptoms: a systematic review and meta-analysis. *Dis Esophagus*. 2017;30(2):1-8.
44. Reimer C, Lødrup AB, Smith G, Wilkinson J, Bytzer P. Randomised clinical trial: alginate (Gaviscon Advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. *Aliment Pharmacol Ther*. 2016;43(8):899-909.
45. McGlashan JA, Johnstone LM, Sykes J, Strugala V, Dettmar PW. The value of a liquid alginate suspension (Gaviscon Advance) in the management of laryngopharyngeal reflux. *Eur Arch Oto-Rhino-Laryngol*. 2009;266(2):243-251.
46. Gyawali CP, Yadlapati R, Fass R, et al. Updates to the modern diagnosis of GERD: Lyon consensus 2.0. *Gut*. 2024;73(2):361-371.
47. Krause AJ, Carlson DA, Chan WW, Chen CL, Gyawali CP, Yadlapati R; Laryngeal Symptoms Working Group. High diagnostic yield of abnormal endoscopic findings in the evaluation of laryngopharyngeal reflux. *Clin Gastroenterol Hepatol*. 2024;22(8):1741-1743.e1.
48. Chen JW, Vela MF, Peterson KA, Carlson DA. AGA clinical practice update on the diagnosis and management of extraesophageal gastroesophageal reflux disease: expert review. *Clin Gastroenterol Hepatol*. 2023;21(6):1414-1421.e3.
49. Borges LF, Chan WW, Carroll TL. Dual pH probes without proximal esophageal and pharyngeal impedance may be deficient in diagnosing LPR. *J Voice*. 2019;33(5):697-703.
50. Hashimoto H, Piskorz MM, Olmos JI, et al. Prolonged wireless pH monitoring increases diagnostic yield in patients with reflux symptoms and borderline 24-hour impedance pH. *Dis Esophagus*. 2025;38(2):doaf030.
51. Klochan CM, Slaughter JC, Trawick EP, Holzman M, Vaezi MF. 687 Fundoplication in patients with extraesophageal reflux (EER) refractory to PPI therapy: trust clinical judgment over impedance or pH. *Gastroenterology*. 2009;136(5):A-107.
52. Palombini BC, Villanova CAC, Araújo E, et al. A pathogenic triad in chronic cough: asthma, postnasal drip syndrome, and gastroesophageal reflux disease. *Chest*. 1999;116(2):279-284.
53. McGarvey LPA, Heaney LG, Lawson JT, et al. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. *Thorax*. 1998;53(9):738-743.
54. Rafii B, Taliercio S, Achlatis S, Ruiz R, Amin MR, Branski RC. Incidence of underlying laryngeal pathology in patients initially diagnosed with laryngopharyngeal reflux. *Laryngoscope*. 2014;124(6):1420-1424.
55. Milstein CF, Charbel S, Hicks DM, Abelson TI, Richter JE, Vaezi MF. Prevalence of laryngeal irritation signs associated with reflux in asymptomatic volunteers: impact of endoscopic technique (rigid vs. flexible laryngoscope). *Laryngoscope*. 2005;115(12):2256-2261.
56. Lechien JR, Schindler A, De Marrez LG, et al. Instruments evaluating the clinical findings of laryngopharyngeal reflux: a systematic review. *Laryngoscope*. 2019;129(3):720-736.
57. Branski RC, Bhattacharyya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. *Laryngoscope*. 2002;112(6):1019-1024.

58. Rosen R, Mitchell PD, Amirault J, Amin M, Watters K, Rahbar R. The edematous and erythematous airway does not denote pathologic gastroesophageal reflux. *J Pediatr*. 2017;183:127-131.
59. Kunsch S, Gross V, Neesse A, et al. Combined lung-sound and reflux-monitoring: a pilot study of a novel approach to detect nocturnal respiratory symptoms in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2011;33(5):592-600.
60. Nieto L, de Diego A, Perpiñá M, et al. Cough reflex testing with inhaled capsaicin in the study of chronic cough. *Respir Med*. 2003;97(4):393-400.
61. Holt KJ, Belcher J, Smith JA. Novel capsaicin cough endpoints effectively discriminate between healthy controls and patients with refractory chronic cough. *Respir Med*. 2023;208:107142.
62. Dulery C, Lechot A, Roman S, et al. A study with pharyngeal and esophageal 24-hour pH-impedance monitoring in patients with laryngopharyngeal symptoms refractory to proton pump inhibitors. *Neurogastroenterol Motil*. 2017;29(1):e12909.
63. Mazzoleni G, Vailati C, Lisma DG, Testoni PA, Passaretti S. Correlation between oropharyngeal pH-monitoring and esophageal pH-impedance monitoring in patients with suspected GERD-related extra-esophageal symptoms. *Neurogastroenterol Motil*. 2014;26(11):1557-1564.
64. Yadlapati R, Adkins C, Jaiyeola DM, et al. Abilities of oropharyngeal pH tests and salivary pepsin analysis to discriminate between asymptomatic volunteers and subjects with symptoms of laryngeal irritation. *Clin Gastroenterol Hepatol*. 2016;14(4):535-542.e2.
65. Wang J, Zhao Y, Ren J, Xu Y. Pepsin in saliva as a diagnostic biomarker in laryngopharyngeal reflux: a meta-analysis. *Eur Arch Oto-Rhino-Laryngol*. 2018;275(3):671-678.
66. Yadlapati R, Kaizer A, Greytak M, Ezekewe E, Simon V, Wani S. Diagnostic performance of salivary pepsin for gastroesophageal reflux disease. *Dis Esophagus*. 2021;34(4):doaa117.
67. Kopec SE, Irwin RS, French CL, Wilson MM, Bol S. Treatment of cough due to gastroesophageal reflux disease (GERD): a double-blind randomized placebo-controlled trial comparing diet and/or cicaprode. *Am J Respir Crit Care Med*. 2001;163(5)(suppl):A64.
68. Smith JE, Morjaria JB, Morice AH. Dietary intervention in the treatment of patients with cough and symptoms suggestive of airways reflux as determined by Hull Airways Reflux Questionnaire. *Cough*. 2013;9(1):27.
69. Steward DL, Wilson KM, Kelly DH, et al. Proton pump inhibitor therapy for chronic laryngo-pharyngitis: a randomized placebo-control trial. *Otolaryngol Head Neck Surg*. 2004;131(4):342-350.
70. Hránková V, Balner T, Kondé A, et al. The role of an anti-reflux diet in the treatment of chronic cough caused by laryngopharyngeal reflux. *Eur Arch Oto-Rhino-Laryngol*. 2025;282(4):2009-2013.
71. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev*. 2011;2011(1):CD004823.
72. Chang AB, Lasserson TJ, Kiljander TO, Connor FL, Gaffney JT, Garske LA. Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. *BMJ*. 2006;332(7532):11-17.
73. Ours TM, Kavuru MS, Schilz RJ, Richter JE. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol*. 1999;94(11):3131-3138.
74. Ribolsi M, Luca Guarino MP, Balestrieri P, et al. The results from up-front esophageal testing predict proton pump inhibitor response in patients with chronic cough. *Am J Gastroenterol*. 2021;116(11):2199-2206.
75. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2022;117(1):27-56.
76. Park W, Hicks DM, Khandwala F, et al. Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. *Laryngoscope*. 2005;115(7):1230-1238.
77. Rohof WO, Bennink RJ, Smout AJPM, Thomas E, Boeckxstaens GE. An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2013;11(12):1585-1591.
78. Samuels TL, Yan K, Patel N, et al. Alginates for protection against pepsin-acid induced aerodigestive epithelial barrier disruption. *Laryngoscope*. 2022;132(12):2327-2334.
79. Tseng WH, Tseng PH, Wu JF, et al. Double-blind, placebo-controlled study with alginate suspension for laryngopharyngeal reflux disease. *Laryngoscope*. 2018;128(10):2252-2260.
80. Barrett CM, Patel D, Vaezi MF. Laryngopharyngeal reflux and atypical gastroesophageal reflux disease. *Gastrointest Endosc Clin N Am*. 2020;30(2):361-376.
81. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9853):1583-1589.
82. Halum SL, Sycamore DL, McRae BR. A new treatment option for laryngeal sensory neuropathy. *Laryngoscope*. 2009;119(9):1844-1847.
83. Weijenborg PW, de Schepper HS, Smout AJPM, Bredenoord AJ. Effects of antidepressants in patients with functional esophageal disorders or gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol*. 2015;13(2):251-259.e1.
84. Jeyakumar A, Brickman TM, Haben M. Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy. *Laryngoscope*. 2006;116(12):2108-2112.
85. Dong R, Xu X, Yu L, et al. Randomised clinical trial: gabapentin vs baclofen in the treatment of suspected refractory gastro-oesophageal reflux-induced chronic cough. *Aliment Pharmacol Ther*. 2019;49(6):714-722.
86. Irwin RS, Madison JM. Unexplained or refractory chronic cough in adults. *N Engl J Med*. 2025;392(12):1203-1214.
87. Kum E, Patel M, Diab N, et al. Efficacy and tolerability of gefapixant for treatment of refractory or unexplained chronic cough: a systematic review and dose-response meta-analysis. *JAMA*. 2023;330(14):1359-1369.
88. Pelleg A, Hurt CM. Mechanism of action of ATP on canine pulmonary vagal C fibre nerve terminals. *J Physiol*. 1996;490(pt 1)(pt 1):265-275.
89. Yoon YH, Park KW, Lee SH, Park HS, Chang JW, Koo BS. Efficacy of three proton-pump inhibitor therapeutic strategies on laryngopharyngeal reflux disease; a prospective randomized double-blind study. *Clin Otolaryngol*. 2019;44(4):612-618.
90. Glicksman JT, Mick PT, Fung K, Carroll TL. Prokinetic agents and laryngopharyngeal reflux disease: prokinetic agents and laryngopharyngeal reflux disease: a systematic review. *Laryngoscope*. 2014;124(10):2375-2379.
91. Lindstrom DR, Wallace J, Loehrl TA, Merati AL, Toohill RJ. Nissen fundoplication surgery for extraesophageal manifestations of gastroesophageal reflux (EER). *Laryngoscope*. 2002;112(10):1762-1765.
92. Eriksson SE, Sarici IS, Zheng P, Gardner M, Jobe BA, Ayazi S. Magnetic sphincter augmentation for laryngopharyngeal reflux: an assessment of efficacy and predictors of outcome [published online April 18, 2024]. *J Voice*. doi:10.1016/j.jvoice.2024.03.026.
93. Sidwa F, Moore AL, Alligood E, Fisichella PM. Surgical treatment of extraesophageal manifestations of gastroesophageal reflux disease. *World J Surg*. 2017;41(10):2566-2571.
94. Lechien JR, Dapri G, Dequanter D, et al. Surgical treatment for laryngopharyngeal reflux disease: a systematic review. *JAMA Otolaryngol Head Neck Surg*. 2019;145(7):655-666.
95. Snow GE, Dbouk M, Akst LM, et al. Response of laryngopharyngeal symptoms to transoral incisionless fundoplication in patients with refractory proven gastroesophageal reflux. *Ann Otol Rhinol Laryngol*. 2022;131(6):662-670.
96. Trad KS, Fox MA, Simoni G, et al. Transoral fundoplication offers durable symptom control for chronic GERD: 3-year report from the TEMPO randomized trial with a crossover arm. *Surg Endosc*. 2017;31(6):2498-2508.
97. Trad KS, Barnes WE, Prevou ER, et al. The TEMPO trial at 5 years: transoral fundoplication (TIF 2.0) is safe, durable, and cost-effective. *Surg Innov*. 2018;25(2):149-157.
98. Hunter JG, Kahrilas PJ, Bell RCW, et al. Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. *Gastroenterology*. 2015;148(2):324-333.e5.
99. Liu K, Krause AJ, Greytak M, Taft T, Walsh E, Yadlapati R. Psychosocial burden in patients with chronic laryngopharyngeal symptoms with and without pathologic acid reflux. *Neurogastroenterol Motil*. 2024;36(9):e14852.
100. Walsh E, Krause AJ, Greytak M, et al. Laryngeal recalibration therapy improves laryngopharyngeal symptoms in patients with suspected laryngopharyngeal reflux disease. *Am J Gastroenterol*. 2024;119(11):2198-2205.
101. Chamberlain Mitchell SAF, Garrod R, Clark L, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. *Thorax*. 2017;72(2):129-136.
102. Keefer L, Ballou SK, Drossman DA, Ringstrom G, Elsenbruch S, Ljótsson B. A Rome Working Team Report on brain-gut behavior therapies for disorders of gut-brain interaction. *Gastroenterology*. 2022;162(1):300-315.
103. Pullerits T, Ternesten-Hasséus E, Johansson EL, Millqvist E. Capsaicin cough threshold test in diagnostics. *Respir Med*. 2014;108(9):1371-1376.
104. Hilton ECY, Baverel PG, Woodcock A, Van Der Graaf PH, Smith JA. Pharmacodynamic modeling of cough responses to capsaicin inhalation calls into question the utility of the C5 end point. *J Allergy Clin Immunol*. 2013;132(4):847-855.e1-5.