Laryngopharyngeal Reflux and Functional Laryngeal Disorder: Perspective and Common Practice of the General Gastroenterologist

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Abstract: Laryngopharyngeal reflux (LPR) is an extraesophageal variant of gastroesophageal reflux disease that is associated with chronic cough, hoarseness, dysphonia, recurrent throat clearing, and globus pharyngeus. Due to nonspecific symptoms, laryngoscopy is often performed to rule out malignancy, and the diagnosis of LPR is considered with any signs of laryngeal inflammation. However, laryngoscopic findings have high interobserver variability, and, thus, most patients are tried on an empiric course of acid-suppressive therapy to see whether symptoms resolve. In this article, which focuses on the perspective and common practice of the general gastroenterologist, we review our understanding of the pathophysiology, diagnosis, and treatment of LPR based on important clinical articles in the gastroenterology literature. We also propose new diagnostic criteria for functional laryngeal disorder and review laryngeal hypersensitivity and treatment options for general gastroenterologists.

Gastroesophageal reflux disease (GERD) is the most prevalent gastrointestinal disorder in the United States, affecting 18% to 28% of the population with an estimated 13% of Americans using medications for GERD at least twice weekly.[1,2] GERD is a spectrum of disease that usually presents clinically with symptoms of heartburn and regurgitation, which are considered to be part of esophageal syndromes, but can also present with extraesophageal manifestations, including symptoms of chronic cough, chronic laryngitis, asthma, chest pain, postnasal drip, or recurrent sinusitis. The evaluation and management of patients who primarily present with extraesophageal reflux (EER)-related symptoms has been increasingly difficult due to a lack of gold-standard testing and lack of reliable data suggesting that treatment of GERD improves clinical outcomes in this patient population.[3] This often leads to high economic and social burdens on patients due to delay in diagnosis, numerous tertiary care referrals, and lack of effective medications. The economic burden of

patients with GERD is estimated to be $9.3 billion[4] to $12.1 billion,[5] but the cost of treating patients with EER is 5 times higher, at approximately $50 billion.[6] The single greatest contributor to the cost of EER management is the use of proton pump inhibitors (PPIs), at 52% of the cost burden.[6]

Laryngopharyngeal reflux (LPR) is an extraesophageal variant of GERD characterized by dysphonia, globus pharyngeus (sensation of a lump in the throat), hoarseness, recurrent throat clearing, and chronic cough. LPR is estimated to account for 10% of all ear, nose, and throat (ENT) clinic patients and 50% of patients with voice complaints.[7] However, due to the lack of gold-standard testing, the prevalence of LPR can be overstated, with one meta-analysis that reviewed data from pH probe readings reporting that 10% to 60% of normal subjects demonstrated reflux.[8,9] The differential for chronic laryngeal inflammation is broad, but acid reflux is usually presumed to be the underlying etiology due to the high prevalence of GERD in the population and the ease of prescribing acid-suppressive therapy. In this article, we highlight the general gastroenterologist's perspective and common practice by reviewing important clinical articles in the gastroenterology literature; examining the pathophysiology, diagnostic testing, and treatment options of LPR; and discussing the role of laryngeal hypersensitivity and new criteria for functional laryngeal disorder.

Pathophysiology of Laryngopharyngeal Reflux

LPR has remained a diagnostic challenge, primarily due to the lack of understanding of the pathophysiology and etiology of the condition. Two mechanisms have been proposed to explain laryngeal manifestations of GERD. The microaspiration theory[10] postulates that there is direct acid-peptic injury to the larynx by esophagopharyngeal reflux, whereas the esophageal bronchial reflex theory[11-13] proposes that acidification of the distal esophagus can induce laryngeal symptoms from a vagally mediated reflex.[9] The larynx is highly innervated, and in a normal individual, any reflux would be sensed and elicit a protective cough. However, this protective mechanism might be altered in patients with LPR, with one study showing decreased laryngeal adductor reflexes in response to endoscopic administration of air pulses in this group of patients.[14] This may lead to increased stasis of injurious agents in the larynx. Animal studies have evaluated the role of gastric agents (acid and pepsin) vs duodenal juices (bile acids and trypsin) in laryngeal tissue, and found that at acidic pH levels, pepsin and conjugated bile acids were the most injurious, leading to erythema and inflammation.[15,16] This led to the idea of using acid-suppressive therapy, which should eliminate the injurious potential of acid reflux. However, studies of human laryngeal tissue have been lacking.

Table 1. Most Common Symptoms Associated With Laryngopharyngeal Reflux[7]

Dysphonia (71%)
Cough (51%)
Globus pharyngeus (47%)
Throat clearing (42%)

More recent studies have evaluated the role of *Helicobacter pylori* in LPR with conflicting results.[17-20] One study showed high *H pylori* positivity among patients with LPR (diagnosed based on a patient-reported outcome measure),[21] but another study showed that there was no significant relationship between the symptoms and *H pylori* positivity.[22] A randomized, controlled trial (RCT) of 212 patients in Egypt found that 57% of patients with LPR had positive *H pylori* stool antigen.[23] The majority of patients (87/90; 96.6%) with negative *H pylori* stool antigen treated with esomeprazole 40 mg daily for 4 weeks reported symptom improvement. Patients with positive *H pylori* stool antigen were randomized to esomeprazole vs triple therapy (esomeprazole, amoxicillin, and clarithromycin). Only 23 of 60 patients with positive *H pylori* stool antigen (38%) had improvement in symptoms with esomeprazole, whereas 53 of 61 patients (87%) reported improvement in symptoms with triple therapy.[23] However, the results of this study are difficult to interpret and might be an outlier given the high response rate (96.6%) with PPI therapy in the non–*H pylori* group, and validated assessment scales were not used. Multiple other studies have failed to find an association between *H pylori* and LPR symptoms,[18,24,25] with a recent systematic review and meta-analysis concluding that there is insufficient evidence to make a recommendation regarding the testing and treatment of *H pylori* in this population.[20]

Diagnostic Conundrum of Laryngopharyngeal Reflux

Most patients with LPR do not have the classic reflux symptoms of heartburn and regurgitation, which often leads to diagnostic ambiguity. Table 1 lists the most common symptoms attributed to LPR.[7] The 2 most common tests used in patients with LPR are laryngoscopy and ambulatory pH monitoring.

Laryngoscopy

Figure 1 shows the laryngoscopic findings commonly attributed to LPR, which include vocal cord edema,

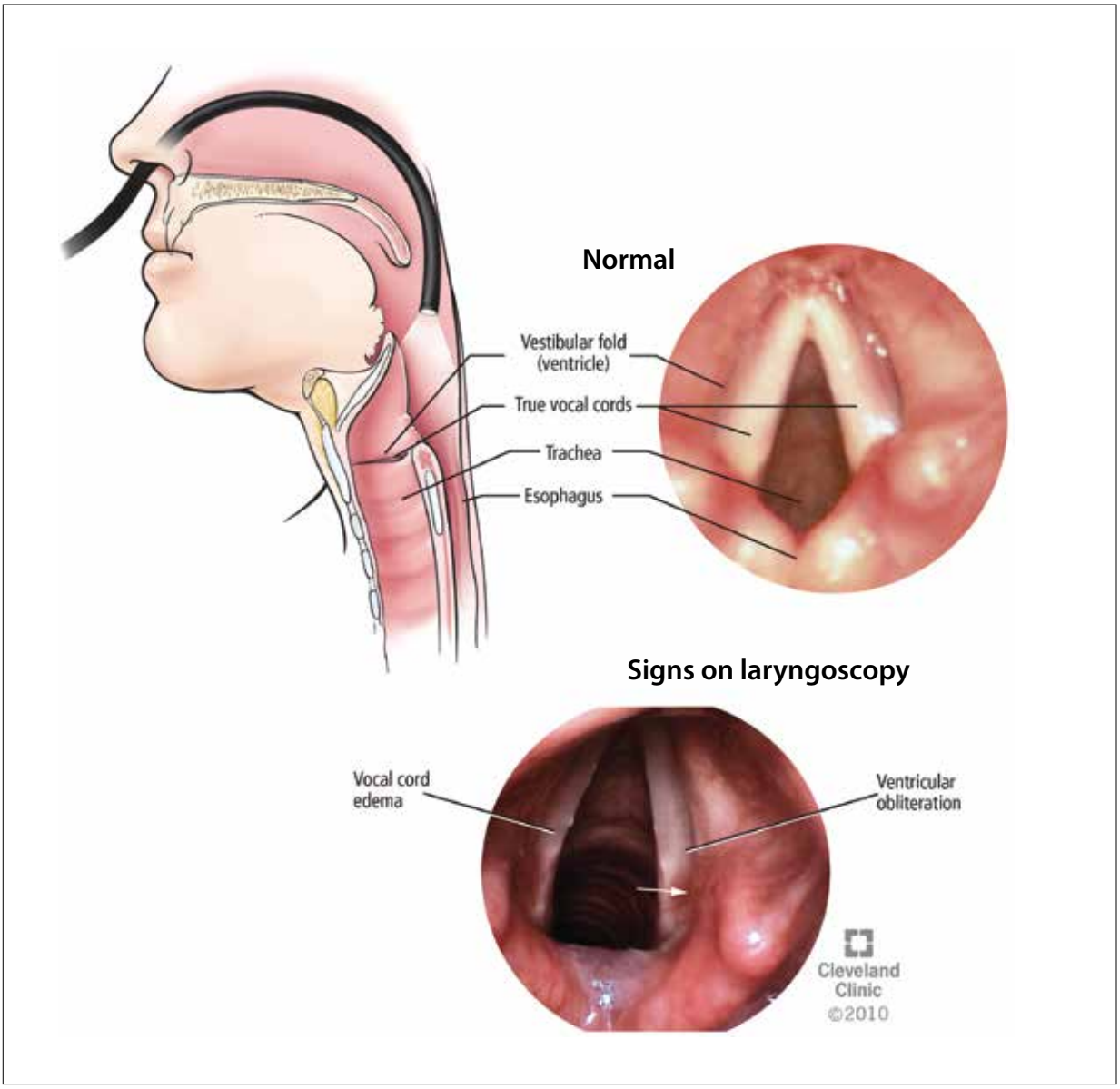

Figure 1. Patients with complaints such as sore throat, hoarseness, cough, dysphasia, chronic throat clearing, and a feeling of a lump in the throat (globus pharyngeus) often undergo laryngoscopy to rule out malignancy and to evaluate for signs of tissue irritation. Once malignancy is ruled out, many patients receive a diagnosis of laryngopharyngeal reflux (LPR). The top of the figure shows normal findings. The bottom shows signs on laryngoscopy. Laryngoscopic signs such as erythema (arrow), edema, ventricular obliteration, postcricoid hyperplasia, and pseudosulcus can be used to diagnose LPR. However, the evidence linking these signs to clinical symptoms is not strong.[3]

erythema, ventricular obliteration, and pseudosulcus ovalis.[3] Of these signs, vocal cord edema was the finding most often used to diagnose LPR in one study.[26] However, these signs have poor reliability and high interobserver variability, which leads to poor sensitivity and specificity.[12,27,28] One study found that over 80% of healthy controls had 1 or more signs of laryngeal irritation on laryngoscopy.[29] Given the high interobserver variability due to nonspecific signs of LPR, there has been an increasing effort into developing a standardized scoring system based on laryngeal findings. Belafsky and colleagues developed the Reflux Finding Score, which is based on 8 laryngoscopic

findings (subglottic edema, ventricular edema, erythema, vocal cord edema, diffuse laryngeal edema, hypertrophy of the posterior commissure, granuloma or granulation tissue, and thick endolaryngeal mucus) and has a score ranging from 0 (best) to 26 (worst).[30] In a series of 40 patients with LPR confirmed by pH monitoring, the authors found that a score higher than 7 had a 95% probability of having LPR.[30] However, other studies have questioned the reliability of this score.[27,31] There is also a disconnect between LPR symptoms and laryngoscopic findings. In one study, patients with LPR symptoms who were refractory to PPI therapy underwent a Nissen fundoplication, and 1 year after the surgery, laryngeal signs improved in 80% of the patients, but symptoms improved in only 10% of them.[32]

One of the primary indications for laryngoscopy in this population is to rule out malignancy, as LPR is a diagnosis of exclusion. There is significant overlap between symptoms of LPR and early laryngeal cancer, and, thus, a careful history and direct laryngeal evaluation are necessary.[33-36] Therefore, along with a careful clinical history (including risk factors for malignancy and a medication review to ensure that the patient is not on an angiotensin-converting enzyme inhibitor), direct laryngoscopy is the first step in the evaluation of any patient with suspected LPR.

Ambulatory pH Monitoring

Ambulatory pH monitoring using a 24-hour transnasal double-probe (simultaneous esophageal and pharyngeal) catheter was previously considered the gold-standard test for detecting reflux; however, it is unreliable in patients with primarily laryngeal symptoms.[9] A systematic review of 11 studies using 24-hour double-probe pH monitoring in patients with LPR and controls found that there was no significant difference in the prevalence of pharyngeal reflux between the 2 groups, and only a minority of patients with clinically diagnosed laryngitis had pharyngeal reflux events.[37] Furthermore, patients with pharyngeal reflux events were no more likely to respond to acid-suppressive therapy than patients with no documented reflux.[38] Another study found that patients with suspected LPR refractory to antisecretory therapy (PPIs) did not exhibit abnormal pharyngeal or esophageal pH-impedance off or on therapy and that LPR was unlikely in the group with prior nonresponse to PPI therapy.[39] Thus, pharyngeal pH monitoring is not routinely used in clinical practice currently with its poor sensitivity (70%-80%) and specificity (false-negative results of 20%-50%).[9,40,41]

One potential explanation for the poor reliability of pharyngeal pH catheters is that the majority of pharyngeal reflux events that lead to laryngitis are caused by aerosolized molecules, which are not detected by the pH catheters.[42] Thus, addressing this limitation, a nasopharyngeal pH monitoring system (Restech Dx-pH Measurement System, Restech Corporation) was recently developed to measure changes in pH in either liquid or aerosolized droplets.[43] In a small pediatric study of patients with suspected LPR, this system was able to detect all patients who had histopathologic changes showing reflux, with 80% of patients either positive by pH probe or by pH probe and biopsy.[44] Other studies comparing reflux events using an esophageal impedance/pH catheter and an oropharyngeal pH probe found significant discordance, with the oropharyngeal pH probe detecting events that did not correlate with reflux episodes on distal esophageal testing.[45-47] Prospective studies are needed to understand the clinical utility of oropharyngeal pH monitoring devices.

Esophageal pH monitoring (using either a wireless or a catheter-based device) is currently considered the gold standard for the evaluation of esophageal acid exposure and diagnosis of GERD.[48] In patients with EER-associated symptoms, there are limited data and no consensus regarding the optimal testing methodology for testing off or on PPI therapy. The current American College of Gastroenterology guidelines recommend that patients with low pretest likelihood of GERD (atypical symptoms without heartburn or regurgitation) should undergo pH testing off acid-suppressive medications; if that testing is negative (showing normal distal esophageal acid exposure), GERD is very unlikely, so PPI therapy can be stopped and diagnostic effort should be focused toward identifying an alternative etiology.[48] Reflux testing on therapy is geared toward the evaluation of nonacid reflux, as one study showed that pH monitoring revealed normal acid exposure in 96% of patients with GERD who were tested on twice-daily PPI therapy.[49]

Impedance Monitoring

Poor sensitivity and reliability of pH monitoring for LPR led to the hypothesis that nonacid reflux might play a role in patients who remain symptomatic after PPI trial. A large multicenter study evaluating patients with primary GERD symptoms (heartburn and regurgitation) and EER symptoms who had undergone multichannel intraluminal impedance-pH (MII-pH) testing found that 10% to 40% of patients on twice-daily PPI therapy might have continued nonacid reflux and some may benefit from antireflux surgery.[50,51] However, in an uncontrolled study in patients with LPR, the predictors for symptom response to antireflux surgery were traditional pH parameters (presence of hiatal hernia, significant reflux at baseline [pH <4 of more than 12% in a 24-hour period], and presence of regurgitation).[52] Impedance monitoring did not predict LPR symptom response in this group of patients.[52] The role of intraluminal impedance monitoring in this population is

currently uncertain due to the lack of treatment implications of nonacid reflux.[9] More recently, we have developed a device that is designed to measure mucosal impedance (MI), or conductivity of the esophageal epithelium. This minimally invasive device can be used through the working channel of an endoscope and provides impedance measurements in the esophagus within seconds. We have shown that MI is able to differentiate between GERD, nonerosive reflux disease, eosinophilic esophagitis, and normal subjects based on the pattern of impedance in the esophagus.[53] In a recent prospective, longitudinal, cohort study involving 41 patients, we have also shown that patients with primarily EER-attributed symptoms had significantly lower MI measurements at 2 cm above the squamocolumnar junction compared to patients without evidence of acid reflux.[54] However, MI has not been evaluated in laryngeal tissue yet. Studies using MI for diagnosis and for predicting treatment response in this group of patients are underway.

Treatment Options for Laryngopharyngeal Reflux

Empiric therapy with twice-daily PPIs is currently considered the best diagnostic and therapeutic test in patients with suspected LPR. A systematic review of 14 uncontrolled studies and 6 placebo-controlled RCTs found that although the uncontrolled trials reported positive results, the RCTs did not show any difference in symptom response with empiric PPI treatment for LPR.[55] A meta-analysis of pooled data from 8 RCTs with a total of 344 patients who had suspected GERD-related chronic laryngitis found similar results, with PPI therapy offering modest but nonsignificant clinical benefit over placebo (relative risk, 1.28; 95% CI, 0.94-1.74).[56] The most recent meta-analysis, which evaluated 14 RCTs with 771 participants, found that patients treated with PPI therapy had a significantly higher response rate compared to those who received placebo (risk difference, 0.15; 95% CI, 0.01-0.30).[57] However, PPI therapy did not show any difference from placebo in the improvement of the Reflux Finding Score.[57] The conflicting results may be due to the lack of a standardized definition for LPR and the lack of a gold-standard diagnostic test, which might lead to the inclusion of patients with nonreflux-related symptoms, possibly negatively affecting the findings. Patients who experience improvement in symptoms with PPI therapy should be weaned to the lowest effective dose.

In patients who do not respond to PPI trial and have negative reflux testing off therapy, it is unlikely that reflux is the etiology of their symptoms, and there should be an evaluation for an alternative etiology using a multidisciplinary approach with ENT, allergy, neurology, and pulmonary specialists based on symptoms. A recent retrospective study involving 35 patients evaluated the efficacy of super high–dose PPI therapy in patients with refractory LPR, and noted modest improvement in laryngeal signs of irritation but no differences in 24-hour pH impedance monitoring.[58] More importantly, the study did not evaluate for any improvement in clinical symptoms, which, as noted previously, does not correlate with improvement in laryngoscopic findings.[32] Research on surgical fundoplication has also shown variable efficacy, ranging from 10% to 93% in uncontrolled studies.[59] One study randomized 100 patients with objective evidence of GERD (DeMeester score ≥14.7 and either a symptom correlation ≥50% or >73 reflux episodes on 24-hour MII-pH monitoring) and extraesophageal symptoms (primarily hoarseness) to floppy Nissen vs Toupet fundoplication, and found improvement in symptom scores at 3- and 12-month follow-up.[60] A prospective observational study evaluated Nissen fundoplication vs PPI therapy for LPR based on oropharyngeal pH monitoring and symptom scale in 31 patients with type I hiatal hernia (at least 2 cm).[61] The authors found that both groups had significant improvement in reflux symptom index (RSI) and LPR symptom scores at 2-year follow-up, but RSI and symptom scores of cough, mucus, and throat clearing were higher in the fundoplication group.[61] Given the lack of high-quality evidence (RCTs) behind fundoplication in this group of patients, precise identification of who might benefit from surgery is critical. Surgical fundoplication should not be offered to patients whose symptoms persist despite PPI therapy, as response rates are poor[32] unless patients have a large hiatal hernia, significant regurgitation, and moderate to severe reflux on pH testing.[52]

Functional Laryngeal Disorder

We propose that functional laryngeal disorder be considered a diagnosis of exclusion in patients who do not have objective findings of reflux on pH testing and in whom other organic etiologies of laryngeal dysfunction have been ruled out. These criteria are similar to the Rome IV criteria for functional disorders, which focus on excluding other etiologies of the symptoms and then making the diagnosis based on the frequency of the symptoms and the impact on daily activities. Laryngeal dysfunction from neurologic disorders such as Parkinson disease, essential tremor, amyotrophic lateral sclerosis, multiple sclerosis, and dystonia should be ruled out.[62] Figure 2 shows a diagnostic and treatment algorithm for general gastroenterologists managing this group of patients.

Studies have proposed that laryngeal hypersensitivity is a common feature of neuropathic laryngeal syndromes with overlapping symptoms such as chronic

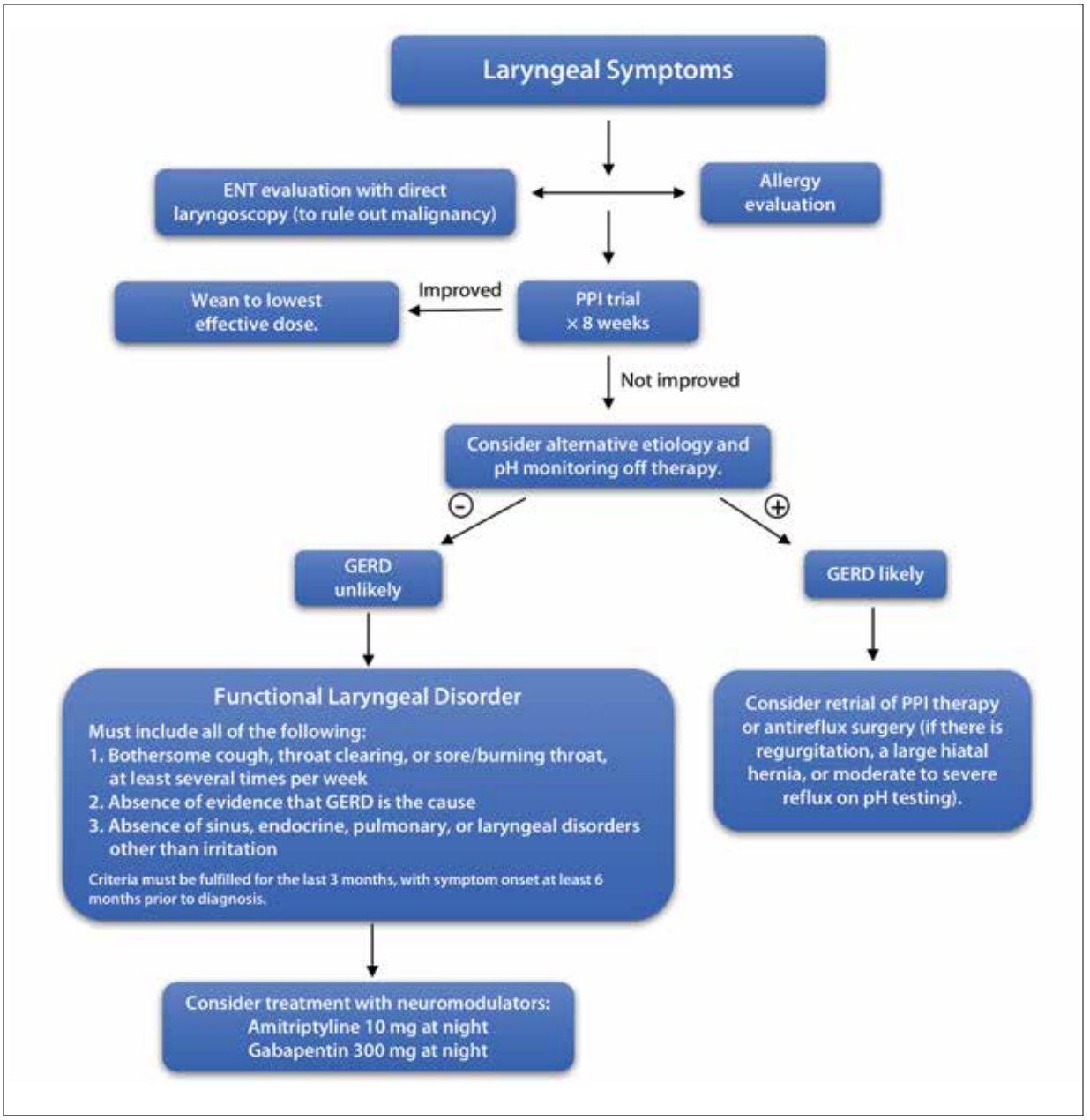

Figure 2. A proposed algorithm for general gastroenterologists for the diagnosis and treatment of patients with laryngeal symptoms.

ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

refractory cough, globus pharyngeus, paradoxical vocal fold movement, and muscle tension dysphonia.[63,64] This has also been frequently classified as the irritable larynx syndrome. It is proposed that certain events might predispose patients to develop laryngeal sensitization, such as an upper respiratory tract infection, an aspiration event, a history of intubation, or other comorbidities, including asthma or chronic rhinosinusitis.[65] Quantitative sensory testing such as capsaicin cough reflex sensitivity, hypertonic saline challenge, the timed swallow test, acoustic voice testing, cough frequency monitor, and the voice stress test have been shown to be significantly impaired in this group of patients.[66] Furthermore, all of the neuropathic laryngeal syndromes not only have significant overlap of symptoms, but have also been shown to have a common sensory dysfunction, supporting the laryngeal

Table 2. Treatment Options for Functional Laryngeal Disorder

Medication	Type of Study	Dose of Medication	Number of Patients	Response Rate
Gabapentin	RCT (primary symptom cough)	Up to 1800 mg/day	62 (32 treatment, 30 placebo)	74%[71]
	Case series (primary symptom cough)	100 to 900 mg/day	28	68%[69]
Pregabalin	Case series (laryngeal symptoms)	75 mg BID, increased to 150 mg BID over 4 weeks	12	83%[74]
Amitriptyline	RCT (primary symptom cough)	10 mg up to 100 mg at night	28 (15 amitriptyline, 13 guaifenesin)	87%[72]
	Case series (primary symptom cough)	10 mg up to 40 mg at night	18	77%[76]

BID, twice daily; RCT, randomized, controlled trial.

hypersensitivity hypothesis.[66] Multiple studies have tried to evaluate the role of laryngeal hypersensitivity with tests using a combination of patient-reported outcome measures such as the Newcastle Laryngeal Hypersensitivity Questionnaire[67] and direct testing using Fiberoptic Endoscopic Evaluation and Sensory Testing[68] or laryngeal electromyography[69]; however, use of these tests in the clinical setting has been limited due to variable sensitivity and specificity, as well as lack of access to some of the equipment and lack of treatment outcome implications.[70] Thus, diagnosis is often made clinically after the exclusion of other etiologies.

Treatment Options for Functional Laryngeal Disorder

The treatment of laryngeal hypersensitivity and functional laryngeal disorder primarily focuses on neuromodulating agents, with most studies directed toward the treatment of chronic cough as the presenting symptom. Gabapentin is the most common agent used in clinical practice and has been studied in a double-blind, placebo-controlled RCT involving 62 patients.[71] Adults with chronic cough of more than 8 weeks' duration were included in the study and randomly assigned to receive gabapentin (up to 1800 mg/day) or placebo for 10 weeks, with the primary endpoint being change in a cough-specific quality-of-life score using the Leicester Cough Questionnaire.[56] Treatment with gabapentin significantly improved cough-specific quality of life compared to placebo, with a number needed to treat of 3.5. The most common side effects were nausea and fatigue, occurring in 31% of patients.[55] A case series involving 28 patients with chronic cough reported improvement in 68% of patients with gabapentin.[69] Another agent that has been studied for chronic cough is amitriptyline. In a RCT of 28 patients with chronic cough (thought to be from postviral vagal neuropathy), patients were randomized to amitriptyline vs cough suppressant for 10 days. The majority of patients treated with amitriptyline had 50% to 100% improvement in cough.[72] A prospective cohort study of 12 patients found similar results with a trial of amitriptyline 10 mg at night resulting in all patients having at least 40% reduction of self-reported symptoms, with most reporting 75% to 100% short-term relief.[73] Pregabalin has been studied in a retrospective case series of 12 patients with various symptoms of laryngeal sensory neuropathy (chronic cough, globus sensation, odynophonia, and/or odynophagia). Treatment with pregabalin started at 75 mg twice daily and increased to 150 mg twice daily if needed for symptomatic relief.[28] The pre- to posttreatment chief complaint symptom severity rating decreased from 3.9/5 to 1.2/5.[74] Given the lack of reliable (RCT) evidence of medications other than gabapentin, American College of Chest Physicians guidelines recently recommended a therapeutic trial of gabapentin for unexplained chronic cough as long as the potential side effects and the risk-benefit profile are discussed with patients prior to use.[75] Table 2 shows the options for neuromodulators. Side effects of all of these medications should be discussed with patients prior to initiation.

Conclusion

The diagnosis and treatment of LPR has been challenging due to the lack of a gold-standard diagnostic test and poor responsiveness to our best available medical therapy (PPIs). Current testing has high interrater variability, leading to overdiagnosis and inappropriate treatment with acid-suppressive medications, resulting in societal and patient burden of cost, frequent referrals to numerous providers, and delay in diagnosis and treatment. Based on our review of important clinical articles in the gastroenterology literature and the common practice of

general gastroenterologists, our approach in patients with suspected LPR starts with a 2-month trial of PPI therapy, and if there is no improvement in symptoms, we recommend that patients undergo pH monitoring off all acid-suppressive therapy. If pH testing is negative, it is unlikely that reflux is the cause of the laryngeal symptoms, and focus should be shifted toward the evaluation of alternative etiologies and treatment of functional laryngeal disorder with the use of neuromodulators.

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