Identifying and Managing Laryngopharyngeal Reflux

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Up to 20% of the US adult population experiences gastroesophageal reflux on a weekly basis.[1] Gastroesophageal reflux disease (GERD) is defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus.[2] Symptoms of GERD include pyrosis (heartburn), regurgitation, dysphagia, cough, and atypical chest pain. Laryngopharyngeal reflux (LPR) is defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the upper airway. Although LPR and GERD are both caused by abnormal reflux of gastric contents, they are distinct clinical entities with differing pathophysiologic mechanisms.

Well-equipped to handle physiologic amounts of gastric reflux, the esophagus has a multi-tiered protective mechanism consisting of a physical antireflux barrier, esophageal acid clearance, and innate tissue resistance.[3] Up to 50 reflux episodes in the esophagus may be considered normal.[4] The larynx, however, lacks both the extrinsic and intrinsic defenses possessed by the esophagus and is much more susceptible to the harmful effects of acid and pepsin. Experiments in animals suggest that as few as 3 reflux episodes a week can produce significant laryngeal damage.[5]

Up to 35% of adults have symptoms suggestive of LPR, such as excessive throat clearing, intermittent dysphonia, the sensation of postnasal drainage (PND), globus, cervical dysphagia, and cough.[6] Many physicians, however, may not recognize the relationship of these symptoms to LPR. The clinician cannot rely upon the presence of heartburn and regurgitation to make the diagnosis of LPR. Instead, a combination of symptoms and findings on laryngoscopy and ambulatory pH monitoring can help establish a diagnosis. This article reviews the signs and symptoms of LPR and outlines an approach to management. Several terms have been used to describe LPR (**Table 1**); *laryngopharyngeal reflux* is the term chosen by the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS)[7] and will be used throughout this article.

TAKE HOME POINTS

- Laryngopharyngeal reflux (LPR) is the backflow of gastric contents above the upper esophageal sphincter into the pharynx.
- Common symptoms of LPR include voice changes, dysphagia, globus, excessive throat mucus and throat clearing, and cough.
- Heartburn and regurgitation are not common complaints in LPR.
- The diagnosis of LPR is based on a constellation of symptoms and laryngoscopic signs. Ambulatory pH testing for LPR must include placement of a probe in the pharynx.
- LPR may require more aggressive treatment than gastroesophageal reflux disease, including twice-daily proton pump inhibitor therapy.

DIAGNOSIS

Symptoms

Symptoms of LPR are diverse and include intermittent dysphonia, chronic throat clearing, excessive throat mucus, sialorrhea, cough, the sensation of PND, cervical dysphagia, dysgeusia, halitosis, throat pain, and the sensation of a lump in the throat (**Table 2**). However, these symptoms are not exclusive to LPR and can be caused by allergy, degenerative neurologic disease, infection, behavioral disorders, medications, and neoplasia. Because these symptoms are nonspecific, the clinician must rely on a combination of symptoms, laryngoscopy findings, pH monitoring, and an empiric

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Table 1. Alternative Names for Laryngopharyngeal Reflux

Extraesophageal reflux
Supraesophageal reflux
Gastroesophagopharyngeal reflux
Reflux laryngitis
Posterior laryngitis
Silent reflux
Atypical reflux disease

Table 2. Symptoms of Laryngopharyngeal Reflux

Intermittent dysphonia
Chronic throat clearing
Excessive throat mucus
Sialorrhea
Cough
Sensation of postnasal drainage
Cervical dysphagia
Dysgeusia
Halitosis
Throat pain
Globus

trial of proton pump inhibitors (PPIs) to make an accurate diagnosis.

Excessive throat mucus and chronic throat clearing are 2 of the most common symptoms of LPR. Acid instilled into the esophagus can result in a rapid increase in salivation;[8] this sudden filling of the mouth with saliva is termed water brash. Bicarbonate found in saliva is effective at neutralizing refluxed gastric acid. Excessive salivation causes a sense of fullness in the pharynx that typically stimulates an individual to clear his/her throat. Excessive throat clearing can lead to hypopharyngeal edema, which causes more secretions to pool in the throat, thus stimulating more throat clearing, and a self-perpetuating cycle ensues. Successful treatment of LPR often relieves the throat clearing and accumulation of excessive mucus.[9] Behavioral modifications are often necessary to address the habitual component involved in cyclical throat clearing.

The sensation of PND is another common symptom attributed to LPR. Patients with PND appear to have more pharyngeal acid exposure than controls.[10] Patients with LPR-related PND often lack other symptoms suggestive of allergic rhinitis, such as rhinorrhea, nasal congestion, sneezing, itchy or runny eyes, and headache. Patients with rhinitis are usually aware of the color and odor of PND, whereas an inability to characterize PND suggests LPR.

LPR can cause the sensation of a foreign body in the throat (ie, globus). The prevalence of globus in the general population may be as high as 16%.[11] Although there are other causes of globus (eg, laryngopharyngeal carcinoma, vallecular cysts, cricopharyngeal dysfunction), reflux may be a causative factor in up to two thirds of individuals with globus.[12] The majority of patients with reflux-related globus will improve with antireflux therapy.[12] Because up to 25% of individuals with globus will have alternative pathology responsible for their symptoms, laryngoscopy is indicated in all persons with the sensation of a lump in their throat (**Figure 1**).

Dysphonia caused by LPR is intermittent. Patients with chronic, unremitting hoarseness are less likely to have reflux as the primary cause of their voice disorder. Similarly, progressive dysphonia is not likely caused by reflux. Atrophy of the vocal folds is part of the normal aging process, with 70% of individuals aged 60 years having significant age-related atrophy (bowing) of their vocal folds.[6] Thus, age is likely a major contributing factor in elderly patients with hoarseness. Dysphonia that is continual and that does not resolve requires early endoscopy to rule out alternative laryngeal pathology. Current or previous tobacco and alcohol use are significant risk factors for laryngeal cancer and are additional indications for early endoscopy.

Symptom Scoring for LPR

Belafsky et al[13] recently developed a 9-item, self-administered, disease-specific outcome instrument for LPR. The Reflux Symptom Index (RSI) is easily administered and highly reproducible and has displayed excellent construct- and criterion-based validity (**Table 3**).[13] Normative data suggest that an RSI score of up to 10 is normal, while a score greater than 13 suggests LPR. The RSI has proven to be useful in establishing the initial diagnosis of LPR, assessing disease severity, and monitoring treatment efficacy. Other symptom scoring systems also have been suggested.[14] These symptom scoring instruments reflect the fact that most patients with LPR will present with a constellation of symptoms rather than an isolated complaint and that symptoms of LPR are distinct from classic GERD symptoms.

Endoscopic Laryngeal Findings

Transnasal fiberoptic laryngoscopy is an essential tool in the evaluation of patients with suspected LPR. The evaluation is performed quickly without sedation but with administration of topical anesthesia and a

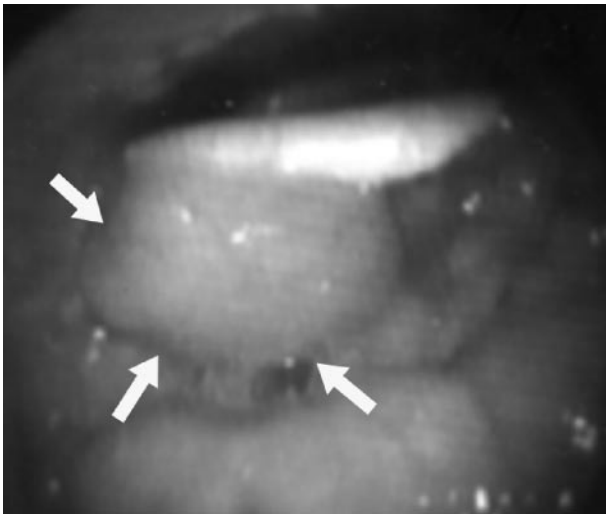

Figure 1. Vallecular cyst (*arrows*) in a patient with a foreign body sensation (globus) in the throat.

Table 3. Reflux Symptom Index

How Do the Following Problems Affect You?	0 = No Problem 5 = Severe Problem					
1. Hoarseness or a problem with your voice	0	1	2	3	4	5
2. Clearing your throat	0	1	2	3	4	5
3. Excess throat mucous or postnasal drip	0	1	2	3	4	5
4. Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
5. Coughing after you ate or after lying down	0	1	2	3	4	5
6. Breathing difficulties or choking episodes	0	1	2	3	4	5
7. Troublesome or annoying cough	0	1	2	3	4	5
8. Sensations of something sticking in your throat or a lump in your throat	0	1	2	3	4	5
9. Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5
	TOTAL					

NOTE: A total score of 10 or less is normal. A total score of 13 or more suggests laryngopharyngeal reflux.

decongestant. The endoscopic laryngeal findings attributable to reflux have been well described[15] and include erythema and edema of the posterior commissure and arytenoid cartilages (**Figure 2**), vocal fold granulomas, nodules, polyps, and possibly carcinoma (**Figure 3**).[16–19]

Belafsky et al[15] developed the Reflux Finding Score (RFS) to quantify and standardize endoscopic findings of LPR. The RFS ranges from a minimum score of zero (no inflammation) to a maximum score of 26; a score greater than 5 suggests the presence of LPR. Other endoscopic laryngeal grading systems have also been proposed.[14,20] It is important to note that these scoring systems are simply a clinical scale of laryngeal inflammation. Infection, allergy, neoplasia, environmental toxins, autoimmune disorders, and vocal misuse and abuse are other potential causes of laryngeal inflammation. For this reason, ambulatory pH testing is frequently employed to assist with the diagnosis of LPR.

Ambulatory pH Monitoring

Typically, reflux testing for GERD involves placing a sensor 5 cm above the upper border of the manometric lower esophageal sphincter. Because distal esophageal pH monitoring does not accurately reflect proximal esophageal or hypopharyngeal pH, a pH sensor must be placed outside of the esophagus 1 cm above the manometric upper esophageal sphincter in order to accurately diagnose LPR (**Figure 4**).

A recent meta-analysis by Merati et al[21] concluded that hypopharyngeal pH monitoring is precise and reliable and accurately differentiates normal patients from those with LPR. Oelschlager et al[22] performed laryngoscopy and hypopharyngeal pH monitoring in persons undergoing antireflux surgery (fundoplication). Eighty-three percent of patients with abnormal laryngeal findings (RFS score > 7) and abnormal findings on hypopharyngeal pH monitoring (≥ 1 episode of pharyngeal reflux on pH monitoring) improved after surgery as compared with 44% of individuals with normal laryngeal findings and normal findings on pH monitoring. The authors determined that laryngoscopy and hypopharyngeal pH monitoring are complementary in the diagnosis of LPR.[22] These data suggest that the gold standard for the diagnosis of LPR may be a combination of extraesophageal pH monitoring, patient symptoms, and laryngoscopy. Patients who have abnormal laryngeal findings and normal findings on pH monitoring may have an alternate cause of laryngeal inflammation. Patients with normal laryngeal findings and abnormal findings on pH monitoring are unlikely to have laryngeal injury from reflux despite the presence of acid in the hypopharynx.

Empiric Medical Trial

Many clinicians consider an empiric trial with PPIs a reasonable approach to the diagnosis of LPR. The current recommendation for an empiric trial is a PPI taken twice daily for up to 3 months.[23] If there is no response to twice-daily PPI therapy after 3 months,

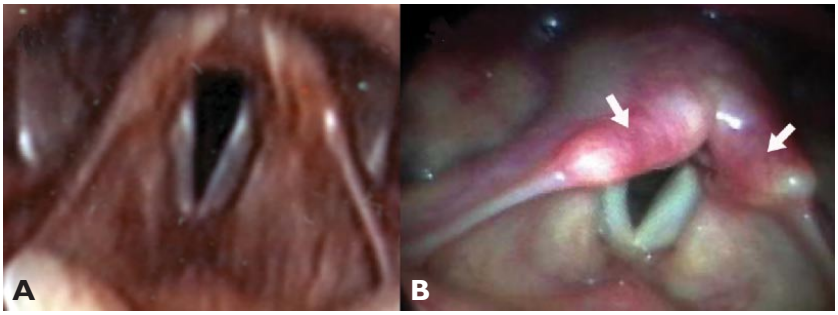

Figure 2. Images of (**A**) a normal larynx on endoscopy and (**B**) isolated arytenoid erythema (*arrows*) in a patient with laryngopharyngeal reflux.

treatment failure or (more likely) an alternative cause for the patient's symptoms should be suspected. Advantages of an empiric PPI trial are its ease of use and sensitivity; however, this approach lacks specificity. There is a strong placebo effect with treatment for reflux disease. In a placebo-controlled study of patients with LPR, symptomatic improvement was seen in 50% of patients who received placebo and lifestyle modification compared with 53% of patients who received PPI therapy and lifestyle modification.[24] Noordzij et al[25] also reported a strong placebo effect for the treatment of LPR. Thus, a significant proportion of individuals who "respond" to an empiric PPI trial may be erroneously diagnosed with reflux disease because of the strong placebo effect.

Esophagoscopy in Patients with LPR

Whether it is necessary to screen patients with LPR for esophageal cancer is currently uncertain. The prevalence of adenocarcinoma of the esophagus (EAC) is increasing more rapidly than the prevalence of any other cancer in the United States.[26] The prognosis of symptomatic EAC is dismal, and the best chance for survival is to diagnose the disease at an early stage. The prevalence of esophagitis and Barrett's esophagus in patients with LPR is 12% and 7%, respectively.[27] There is debate among experts about whether these numbers warrant esophagoscopy for all persons with LPR. Reavis et al[28] reported that symptoms of LPR, particularly cough, better predict the presence of EAC than typical GERD symptoms: 57% of patients with EAC never experienced heartburn or regurgitation, while chronic cough was an independent risk factor for the development of EAC. Thus, symptoms of LPR may be the only warning signs of esophageal disease.

With the advent of unsedated transnasal esophagoscopy (TNE), the esophagus can be evaluated comfortably in the office without anesthesia.[29] To our knowledge, no serious complications from TNE have been reported. Based on the Reavis et al[28] data and the safety and efficacy of TNE, it is our practice to screen most patients with documented LPR for esophageal cancer. Warning signs necessitating early endoscopy include dysphagia, cough, bleeding, choking, chest pain, and weight loss.

TREATMENT

Patients with LPR are often referred to the otolaryngologist, pulmonologist, or gastroenterologist, and management is frequently multidisciplinary. Treatment of LPR is tailored to the individual patient. Postma et al[30] have categorized LPR into minor, major, and life-threatening forms. Patients with minor LPR have symptoms that are bothersome but not life-altering. Persons with major LPR have symptoms that significantly impact their quality of life or work performance. For instance, reflux-related dysphonia may be classified as minor LPR in a machinist but as major LPR in a professional singer. Life-threatening LPR is associated with reflux-attributed airway stenosis or spasm, dysplasia, and carcinoma.

Minor LPR

In patients with minor LPR, it is reasonable to start with a step-up therapeutic approach. Our initial approach is with dietary and lifestyle modifications, including weight loss, exercise, smoking cessation, and reduced alcohol, carbonated beverage, and caffeine consumption. Patients are also instructed to avoid tight-fitting clothing, refrain from food and drink for 3 hours before sleep, and elevate the head of the bed, preferably with a bed wedge. For patients with minor LPR who fail to respond to behavioral modifications, antacids or histamine$_2$ (H_2)-receptor antagonists may be used. Sodium alginate forms a physical barrier on the top of the stomach to prevent the regurgitation of stomach contents into the esophagus. It has been shown to significantly decrease the number of reflux episodes, the height of reflux episodes, and the percentage of time esophageal pH is less than 4.0.[31] Sodium alginate may be used as adjunctive therapy for any type of LPR or as sole therapy in minor LPR.

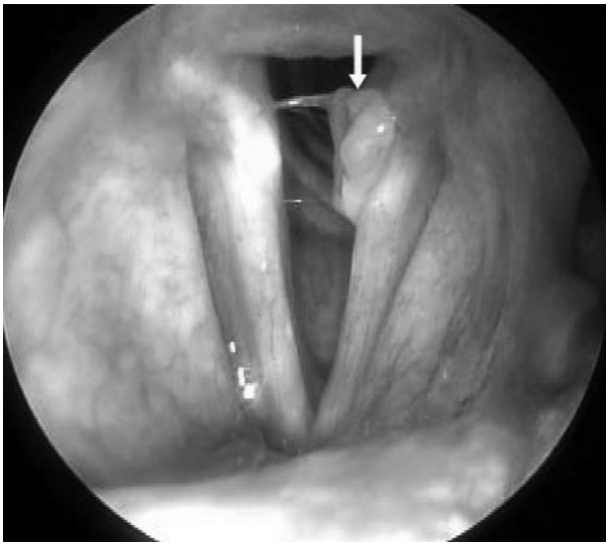

Figure 3. Left vocal process granuloma (*arrow*) in a patient with laryngopharyngeal reflux.

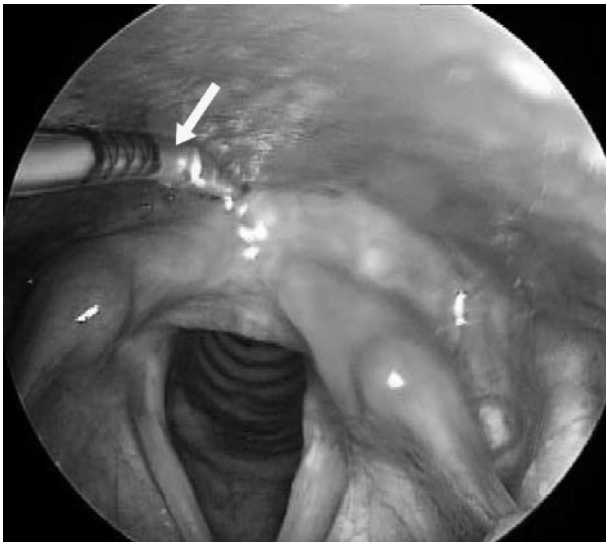

Figure 4. Hypopharyngeal pH sensor (*arrow*) placed 1 cm above the upper esophageal sphincter.

Major LPR

A more aggressive treatment approach is employed for patients with major LPR. Dietary and lifestyle modifications in addition to treatment with a PPI is recommended. The AAO–HNS currently recommends treatment for LPR with twice daily PPI therapy.[7] Although once-daily PPI therapy heals peptic esophagitis in the majority of individuals, twice-daily PPI therapy is often necessary to heal the more delicate laryngeal epithelium. After 2 months of PPI therapy in individuals with suspected LPR, 28% experienced symptom improvement with once-daily dosing compared with 50% with twice-daily dosing. After 4 months of twice-daily PPI therapy, 70% of patients responded.[23] Thus, twice-daily PPI therapy for at least 4 months is a reasonable treatment for major LPR. Symptoms should improve by 2 months. Laryngeal inflammation may continue to resolve after more than 6 months.[32] Twice-daily PPI therapy should be continued until laryngeal examination is normal, at which time the medication can be tapered. Treatment with a maintenance dose of PPI may be required if symptoms or laryngeal findings recur.

Ambulatory pH monitoring is warranted for patients who do not respond to twice-daily PPI therapy. We prefer to perform a baseline pH study off antireflux medication (patients should be off therapy for at least 1 week prior to testing). If the initial ambulatory pH test is abnormal and the individual did not improve with twice-daily PPI therapy, a second pH study on medication is indicated to rule out treatment failure and/or PPI resistance. If the second ambulatory pH study is normal, alternative causes of the patient's symptoms should be sought.

Life-Threatening LPR

All patients with suspected life-threatening LPR should undergo ambulatory pH monitoring to help establish the initial diagnosis and guide appropriate therapy. Twice-daily medical therapy with a PPI should be initiated, and ambulatory pH monitoring should be repeated while the patient is on medication to ensure adequate acid suppression. Strict adherence to behavioral and lifestyle modifications is imperative. Supplemental sodium alginate and an H_2-receptor antagonist at night are often employed. The efficacy of laparoscopic Nissen fundoplication has been proven in patients with LPR.[33–36] For young, healthy patients with life-threatening LPR, many clinicians consider fundoplication to be the treatment of choice.[33–36]

NOCTURNAL REFLUX

There has been increasing interest in reflux symptoms that occur during sleep, especially in patients with apparent PPI treatment failure. Nocturnal acid breakthrough may occur in up to 70% of patients with GERD,[37] but the importance of this phenomenon is unclear in patients with LPR.[38] LPR classically has been described as occurring in the upright position during the daytime, and LPR symptoms (eg, cough) at night may be attributable to gastroesophageal reflux rather than true LPR events. Because none of the available PPIs provides 24-hour acid suppression, the AAO–HNS

recommends treating LPR with twice-daily dosing for optimal acid suppression.[7] To better control nocturnal acid breakthrough, the addition of H_2-blockers administered before bedtime has been suggested.[37] Obstructive sleep apnea (OSA) is strongly associated with GERD,[38] and recent investigations have suggested that LPR is also common in patients with OSA.[39] However, the potential association between LPR and OSA needs to be further investigated.

CONCLUSION

LPR is a symptom complex that has been associated with intermittent dysphonia, chronic cough, globus, throat clearing, the sensation of PND, and excessive throat mucus. Modalities used to diagnose LPR include validated patient symptom scores, findings on fiberoptic laryngoscopy, ambulatory pH monitoring, and an empiric PPI trial. Many consider a combination of patient symptoms, laryngoscopy, and hypopharyngeal pH monitoring to be the diagnostic gold standard. Treatment of LPR is tailored to the individual and includes dietary and behavioral modifications, antacids, sodium alginate, PPIs, H_2-blockers, and fundoplication. **HP**

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