Evaluation and Management of Laryngopharyngeal Reflux

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LARYNGOPHARYNGEAL REFLUX (LPR) is the result of retrograde flow of gastric contents to the laryngopharynx, where it comes in contact with tissues of the upper aerodigestive tract. It has been reported in up to 10% of patients presenting to an otolaryngologist's office, and more than 50% of patients with hoarseness have been found to have reflux-related disease. There is a danger in failing to recognize LPR, while overdiagnosis of LPR can lead to unnecessary costs and missed diagnoses. When a medical practitioner fails to recognize LPR, patients have prolonged symptoms and delayed healing. Inflamed laryngeal tissues are more easily damaged from intubation, have a greater risk of progressing to symptomatic subglottic stenosis and lower airway disease. In a recent report, LPR symptoms were found to be more prevalent in patients with esophageal adenocarcinoma than were typical gastroesophageal reflux symptoms, and they often represented the only sign of disease. Heightened awareness of LPR can lead to overdiagnosis of the condition because the typical LPR symptoms (excessive throat clearing, cough, hoarseness, and globus pharyngeus [a sensation of a lump in the throat]) are nonspecific and can also be caused by infections, vocal abuse, allergy, smoking, inhaled environmental irritants, and alcohol abuse.

Context Laryngopharyngeal reflux (LPR) is a major cause of laryngeal inflammation and presents with a constellation of symptoms different from classic gastroesophageal reflux disease.

Objective To provide a practical approach to evaluating and managing cases of LPR.

Evidence Acquisition The PubMed database and the Ovid Database of Systematic Reviews were systematically searched for laryngopharyngeal reflux, laryngopharyngeal reflux fundoplication, laryngopharyngeal reflux PPI treatment, and gastroesophageal reflux AND laryngitis. Pertinent subject matter journals and reference lists of key research articles were also hand-searched for articles relevant to the analysis.

Evidence Synthesis Reflux of gastric contents is a major cause of laryngeal pathology. The pathophysiology and symptom complex of LPR differs from gastroesophageal reflux disease. Laryngeal pathology results from small amounts of refluxate—typically occurring while upright during the daytime—causing damage to laryngeal tissues and producing localized symptoms. Unlike classic gastroesophageal reflux, LPR is not usually associated with esophagitis, heartburn, or complaints of regurgitation. There is no pathognomonic symptom or finding, but characteristic symptoms and laryngoscopic findings provide the basis for validated assessment instruments (the Reflux Symptom Index and Reflux Finding Score) useful in initial diagnosis. There are 3 approaches to confirming the diagnosis of LPR: (1) response of symptoms to behavioral and empirical medical treatment, (2) endoscopic observation of mucosal injury, and (3) demonstration of reflux events by impedance and pH-monitoring studies and barium swallow esophagram. While pH monitoring remains the standard for confirming the diagnosis of gastroesophageal reflux, the addition of multichannel intraluminal impedance technology improves diagnostic accuracy for describing LPR events. Ambulatory multichannel intraluminal impedance assessment allows for identification of gaseous as well as liquid refluxate and detection of nonacid reflux events that are likely significant in confirming LPR. Although some patients respond to conservative behavioral and medical management, as is the case with gastroesophageal reflux, most require more aggressive and prolonged treatment to achieve regression of symptoms and laryngeal tissue changes. Surgical intervention such as laparoscopic fundoplication is useful in selected recalcitrant cases with laxity of the gastroesophageal sphincter.

Conclusions Laryngopharyngeal reflux should be suspected when the history and laryngoscopy findings are suggestive of the diagnosis. Failure to respond to a 3-month trial of behavioral change and gastric acid suppression by adequate doses of proton pump inhibitor medication dictates need for confirmatory studies. Multichannel intraluminal impedance and pH-monitoring studies are most useful in confirming LPR and assessing the magnitude of the problem.

EVIDENCE ACQUISITION

The PubMed database was systematically searched using the natural language phrases laryngopharyngeal reflux, laryngopharyngeal reflux fundoplication, and laryngopharyngeal reflux PPI treatment. These phrases were

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used individually, with no language or date restrictions. PubMed was then searched using the Medical Subject Heading terms *gastroesophageal reflux* and *laryngitis*. These terms were combined using the AND operator and were limited by language to English, by date range to 2001-2005, and by publication type to randomized controlled trial OR clinical trial. The Ovid version of the Cochrane Database of Systematic Reviews was also searched using the key-word combination of *laryngitis.mp* and *reflux.mp*.

All retrieval sets generated by the PubMed and Ovid searches were reviewed for relevant citations addressing core issues of diagnosis, assessment, and management. The reference lists of all relevant citations were reviewed for further material describing validation of diagnostic instruments and basic science addressing pathogenesis and evolving technology. References in the Cochrane Database of Systematic Reviews protocol for reviewing acid reflux treatment of hoarseness were particularly useful.

**EVIDENCE SYNTHESIS**

Pathogenesis

Laryngopharyngeal reflux differs from gastroesophageal reflux disease (GERD) in that it is often not associated with heartburn and regurgitation symptoms.8 The larynx is vulnerable to gastric reflux, so patients often present with laryngopharyngeal symptoms in the absence of heartburn and regurgitation.8 There are 4 physiological barriers protecting the upper aerodigestive tract from reflux injury: the lower esophageal sphincter, esophageal motor function with acid clearance, esophageal mucosal tissue resistance, and the upper esophageal sphincter.1 The delicate ciliated respiratory epithelium of the posterior larynx that normally functions to clear mucus from the tracheobronchial tree is altered when these barriers fail, and the resultant ciliary dysfunction causes mucus stasis.9 The subsequent accumulation of mucus produces postnasal drip sensation and provokes throat clearing. Direct refluxate irritation can cause coughing and choking (laryngospasm) because sensitivity in laryngeal sensory endings is up-regulated by local inflammation.9 This combination of factors can lead to vocal fold edema, contact ulcers, and granulomas that cause other LPR-associated symptoms: hoarseness, globus pharyngeus, and sore throat.1

Recent investigations suggest that vulnerable laryngeal tissues are protected from reflux damage by the pH-regulating effect of carbonic anhydrase in the mucosa of the posterior larynx.10 Carbonic anhydrase catalyzes hydration of carbon dioxide to produce bicarbonate; this protects tissues from acid refluxate. In the esophagus, there is active production of bicarbonate in the extracellular space that functions to neutralize refluxed gastric acid. There is no active pumping of bicarbonate in laryngopharyngeal epithelium and carbonic anhydrase isoenzyme III, expressed at high levels in normal laryngeal epithelium, was absent in 64% (47/75) of biopsy specimens from laryngopharyngeal tissues of LPR patients.11

**Diagnosis**

History. It is important for physicians to appreciate the potential significance of hoarseness and the relative nonspecificity of laryngitis. Laryngitis is a nonspecific designation of laryngeal inflammation.12 Often, it is mild and resolves spontaneously. When persistent, laryngitis must be further defined based on probable etiologic factors: viral or bacterial infection, allergy, vocal trauma, postnasal discharge, or LPR (Table). Persistent or progressive hoarseness lasting beyond 2 to 3 weeks requires examination of the laryngopharynx to rule out cancer and other serious conditions. This is generally considered good practice; however, laryngeal examination is particularly important in suspected LPR because of the apparent known association of LPR and upper aerodigestive tract cancer.13

Laryngopharyngeal reflux should be suspected when clinical history and initial findings are suggestive. Failure to appreciate LPR as different from GERD has been a major source of skepticism about the diagnosis in the past. Koufman1 was the first to clearly distinguish LPR from GERD, noting that in a combined reported series of 899 patients, throat clearing was a complaint of 87% of LPR patients vs 3% of those with GERD, while only 20% of LPR patients complained of heartburn vs 83%
greater than 13 is considered abnormal. When hoarseness is a prominent symptom, acoustic voice analysis measuring frequency, intensity, perturbation, and signal-to-noise ratio provides an objective way to document symptom severity and progress of the disease.2

Laryngoscopy. Nonspecific signs of laryngeal irritation and inflammation are usually seen, but several findings are highly suggestive of LPR. Although not pathognomonic, thickening, redness, and edema concentrated in the posterior larynx—“posterior laryngitis”—is a common finding.7 Based on a color analysis, Hanson and Jiang8 quantified the degree of erythema as a measure of posterior laryngitis. Other laryngoscopic findings have a strong association with LPR. Contact granuloma was found to be associated with pH monitoring–confirmed cases of LPR in 65% to 74% of patients.16,17 Frequently, the medial edge of the vocal fold appears to have a linear indentation due to diffuse infraglottic edema (Figure 1). Although this gives the illusion of a pathological condition of the vocal fold called sulcus vocalis, in which there is a medial edge concavity of the vocal fold (sulcus) due to fibrosis and tissue loss, it lacks the fibrotic changes of pathological sulcus vocalis.18 This finding is termed pseudosulcus and has been reported in as much as 90% of LPR cases.19 In a comparison of 30 LPR patients and 30 controls, those with pseudosulcus were 2.3 times more likely to have pH testing–confirmed LPR (P<.001).20 Although the sensitivity and specificity of finding pseudosulcus in LPR patients were only 75% and 77%, respectively, pseudosulcus remains highly suggestive of LPR.

Since there is no pathognomonic LPR finding, Belafsky et al21 developed an 8-item clinical severity scale for judging laryngoscopic findings, the Reflux Finding Score, which appears to be useful for assessment and follow-up of LPR patients. They rated 8 LPR-associated findings on a variably weighted scale from 0 to 4: subglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma, and thick endolaryngeal edema. The results could range from 0 (normal) to 26 (worst possible score). Based on their analysis, one can be 95% certain that a patient with a Reflux Finding Score of 7 or more will have LPR.

Confirming Reflux. There are 3 approaches to confirming the diagnosis: response of symptoms to behavioral and empirical medical treatment, endoscopic observation of mucosal injury, and demonstration of reflux events by multichannel monitoring studies. Additional studies, including manometry, spectrophotometric measurement of bile reflux, and mucosal biopsy, can provide information useful in targeting therapy.

Because many patients respond well to behavioral modification and initial medical management, an acid suppression trial is a frequently used approach to initial diagnosis.22 The mainstay of empirical treatment is proton pump inhibitor (PPI) medication for at least 3 months.

Endoscopic examination should include flexible or rigid laryngoscopy in all suspected cases. Transnasal esophagoscopy and esophagogastroduodenoscopy (EGD) are useful in detecting characteristic associated mucosal injury, esophagitis, and Barrett esophagus. Overall, EGD and 24-hour pH-monitoring studies have proven less useful in detecting LPR than in identifying GERD. While EGD reveals esophageal lesions in 50% of typical GERD patients, it is abnormal in less than 20% of LPR laryngitis patients.23 Demonstration of reflux events is best achieved with ambulatory multichannel intraluminal impedance (MCCI) and pH-monitoring studies.24 This approach is based on changes in resistance to alternating current between a series of metal electrodes produced by intraluminal gas, liquid, or bolus. When combined with pH transducers, it makes it possible to give a more complete description of reflux events.25 Not only can acid and nonacid reflux events

Figure 1. Reflux-Induced Granulomas and Pseudosulcus

This rigid telescope view shows a larynx with large bilateral granulomas based on the medial surfaces of the arytenoids (top). A prominent pseudosulcus is identified (arrowhead), representing typical infraglottic edema associated with laryngopharyngeal reflux.

in the GERD group. An international survey of American Bronchoesophageal Association members revealed that the most common LPR symptoms were throat clearing (98%), persistent cough (97%), globus pharyngeus (95%), and hoarseness (95%).14 Based on a careful study of pH probe–confirmed LPR cases, Belafsky et al15 developed a useful self-administered tool, the Reflux Symptom Index, that can help clinicians assess the relative degree of LPR symptoms during initial evaluation and after treatment. Patients are asked to use a 0- to 5-point scale to grade the following symptoms: (1) hoarseness or voice problem, (2) throat clearing, (3) excess throat mucus or postnasal drip, (4) difficulty swallowing, (5) coughing after eating or lying down, (6) breathing difficulties or choking spells, (7) troublesome or annoying cough, (8) sensation of something sticking or a lump in the throat, and (9) heartburn, chest pain, indigestion, or stomach acid coming up. The Reflux Symptom Index score in untreated LPR patients was significantly higher than in controls (21.2 vs 11.6; P<.001). Since the 95% upper confidence limit for controls was 13.6, a Reflux Symptom Index score of 7 or more will have LPR.
be detected but, also, liquid (decreased impedance) as well as gaseous (increased impedance) events can be identified. Although controversy exists, an LPR event is evident when pH in the proximal sensor abruptly drops to less than 4 during or immediately after distal acid exposure (exposure near the lower esophageal sphincter) and LPR is confirmed when total acid exposure time (percentage of time during 24-hour monitoring when the sensor detects pH levels <4) is more than 1%. Reflux is often associated with esophageal dysmotility, including nonprogressive (tertiary) contractions, increased amplitude and duration of contractions, and increased tone. Multichannel intraluminal impedance software technology combined with manometry allows for graphic displays of simulated esophageal motility, sphincter competence, and bolus transport, so the use of barium swallow studies is more limited in LPR assessment.

Treatment

Patient Education and Behavioral Change. Patients with LPR should be educated as to the nature of the problem and counseled on helpful behavioral and dietary changes. Important behavioral changes include weight loss, smoking cessation, and alcohol avoidance. Ideal dietary changes would restrict chocolate, fats, citrus fruits, carbonated beverages, spicy tomato-based products, red wines, caffeine, and late-night meals. Such behavioral changes appear to be an independently significant variable in determining response to medical therapy. Education should include the optimal schedule for taking PPI medications (omeprazole, esomeprazole, rabeprazole, lansoprazole, and pantoprazole), which work best when taken 30 to 60 minutes before meals.

Medical Management. There are 4 categories of drugs used in treating LPR: PPIs, H₂-receptor antagonists, prokinetic agents, and mucosal cytoprotectants. Proton pump inhibitors are considered the mainstay of medical treatment, although there is some controversy regarding their efficacy. A 3-month empirical trial is a cost-effective approach to initial assessment and management. Responders can be weaned, while nonresponders should undergo studies to confirm LPR.

Other drugs have been used to treat LPR. Ranitidine has proven a more potent inhibitor of gastric secretion than cimetidine and is the H₂-receptor antagonist of choice, although it has been found to be of limited value in treating LPR. Prokinetic agents that accelerate esophageal clearance and increase lower esophageal sphincter pressure have fallen out of favor because of reported adverse effects of ventricular arrhythmias and diarrhea. Cisapride has been discontinued because of such serious adverse effects. Tegaserod is a prokinetic agent that was recently demonstrated to decrease reflux and lower esophageal sphincter relaxation events and that we have found useful in treating some LPR cases with associated esophageal dyskinesia. Sucralfate is a polysulfated salt of sucrose that may be helpful as an adjunct in protecting injured mucosa from harmful effects of pepsin and acid. Antacids (sodium bicarbonate-, aluminum-, and magnesium-containing over-the-counter antacids) may relieve GERD symptoms but do not play a role in LPR management.

Surgery. When medical management fails, patients with demonstrable high-volume liquid reflux and lower sphincter incompetence are often candidates for surgical intervention. Fundoplication, either complete (Nissen or Rossetti) or partial (Toupet or Bore), is the most common procedure performed, and the laparoscopic approach is preferred. The goal of surgery is to restore competence of the lower esophageal sphincter, and the outcome measures for LPR include demonstration of reduced pharyngeal reflux episodes. Excellent results have been reported in 85% to 95% of reflux cases but results with LPR are not as impressive. Focusing on a carefully screened group of patients with demonstrable extraesophageal reflux (LPR), Oelschlager et al reported a significant decrease in pharyngeal reflux (7.9 to 1.6 episodes per 24 hours; P<.05) and esophageal acid exposure (7.5% to 2.1%; P<.05) following basic laparoscopic Nissen fundoplication surgery. Fundoplication appears superior to medical management in preventing Barrett metaplasia. Although there is interest in recent nonfundoplication endoscopic techniques (Bard EndoCinch System for endoluminal plication, C. R. Bard, Murray Hill, N J; Stretta System for radiofrequency-induced thermal injury, Curon Medical, Fremont, Calif; and Enteryx liquid polymer injection, Boston Medical, Natick, Mass) to improve lower esophageal sphincteric function, there are no controlled studies and there is no long-term follow-up evidence to support their use.

CONTROVERSIES

While there is an increased appreciation of LPR as distinct from GERD, controversy remains regarding how to confirm the diagnosis and what comprises appropriate medical management. In mild LPR cases, symptoms and physical findings lack sufficient specificity; similar symptoms can result from smoking, toxic inhalants, allergies, and postnasal discharge. Assessing treatment regimens is complicated because clinical trials are vulnerable to placebo effect, uncontrolled behavioral changes, and the variable natural history of LPR. Apparently, 25% of LPR patients experience spontaneous resolution of symptoms and 50% have a chronic course of disease, with intermittent exacerbations and remissions.

Physical Findings

Laryngoscopic findings can be misleading, as shown in several studies in which asymptomatic participants revealed findings similar to those seen in LPR-proven patients. Lundy et al found posterior erythema in 73% of asymptomatic singing students and Hicks et al found tissue changes associated with LPR in a group of more than 100 asymptomatic volunteers. Lack of a reliable clinical marker has confounded progress in the diagnosis and treat-
ment of LPR. Some trials based on clinical diagnosis have been misinterpreted because of lax inclusion criteria. The symptoms and physical findings of mild LPR can be confused with other laryngeal inflammations and non-pathological variations. Since patients with advanced LPR and obvious posterior laryngitis probably differ from patients with milder cases that might have alternative etiologies; future efficacy studies should be rigorous in their exclusion criteria and/or stratify patients in the treatment group. A breakthrough in LPR diagnosis may evolve from recent immunohistochemical studies of laryngeal biopsy specimens showing concentration of pepsin and depletion of carbonic anhydrase isoenzyme III in documented LPR cases.

**pH Monitoring**

Hydrogen ion concentration monitoring is considered the gold standard in detecting GERD, but it is less reliable in confirming LPR. Variability in testing methods and lack of agreement on normative values have raised questions about the sensitivity of pH-monitoring studies for detecting LPR. In some studies, the proximal probe was placed below the upper esophageal sphincter and in others in the hypopharynx, where it is considered closer to the site of injury. High placement of the proximal probe is subject to spurious drops in pH related to the wide-open pharynx and intermittent probe drying. The recently developed Bravo wireless pH-monitoring system (Medtronic Inc, Shoreview, Minn) allows for precise endoscopic placement of the pH transducer at the upper esophageal sphincter. A pinch of esophageal mucosa is used to secure the Bravo capsule, and the patient wears a pager-sized monitor during 48 hours of normal activity. The capsule passes in 3 to 5 days with the superficial sloughing of mucosa. This has been proven more effective in children and some adults who fail to tolerate an external catheter.

Disagreement about normative values adds to the controversy. An abrupt decrease in pH to less than 4 in the proximal probe following or synchronous with a drop at the lower esophageal sphincter is considered a default cutoff value, but this is largely based on lower esophageal standards applied to GERD. In the hypopharynx, a drop to less than 5 is probably a more reliable indicator of proximal reflux because neutralizing factors such as saliva and airway secretions can raise pH values. Failure to demonstrate clinical correlation in pH studies can result from not recognizing the minimal amount of gastric reflux necessary to cause laryngeal inflammation (in patients with LPR) or from not considering alternative sources of laryngeal inflammation in control groups.

An important recent meta-analysis of 16 double pH-probe studies showed consistency and accuracy in distinguishing healthy persons vs those with LPR where techniques were tightly controlled. Upper probe placement at 2 cm above the upper esophageal sphincter was considered critical; higher placement reduces contact of the sensor with mucosa, drying, and false-positive readings, whereas events at or below the sphincter fail to correlate with LPR symptoms. This study affirmed that while healthy persons experienced some reflux events, the acid exposure time percentage is very reliable in differentiating persons with and without LPR. Using a mixed-effects model, LPR was found to be a statistically significant risk
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RecommendaTions

The algorithm in FIGURE 2 summarizes an approach to assessment and management of LPR-induced hoarseness. It begins with clinical evaluation and progresses to an empirical trial of lifestyle and dietary changes and initiation of PPI therapy. Although most patients can experience symptomatic improvement in 3 months, it often takes at least 6 months for the laryngeal symptoms and related physical findings to resolve. Unlike GERD, treatment for LPR must be more aggressive and prolonged in many cases to achieve resolution. Patients whose LPR has resolved should have drugs titrated off, while others who show signs of improvement should be treated with omeprazole, 40 mg (or an equivalent PPI), twice daily 30 to 60 minutes before meals.

Cases that fail to substantially improve with aggressive medical management over 3 months require definitive assessment. Ambulatory MCII with pH monitoring is currently the most effective way to demonstrate LPR. Where such technology is not available, multichannel pH monitoring remains a well-tested option. Mucosal injury, hiatal hernia, and other esophageal pathologies such as Barrett esophagus should be documented by esophagoscopy (transnasal esophagoscopy or EGD). Barium swallow esophagoscopy, manometry, and MCI with manometry can be helpful in demonstrating pathology, describing dysmotility problems, and guiding the surgeon in planning fundoplication surgery. Patients whose LPR fails to resolve after definitive medical or surgical treatment must be followed indefinitely with careful examination of the upper aerodigestive tract for signs of complications and malignancy.

Factor for experiencing objective reflux events (odds ratio, 9.19; 95% confidence interval, 5.4–15.4; P < .001).

Another problem with standard pH probe–monitoring studies is failure to account for bouts of potentially harmful gaseous and/or nonacid refluxate. This is where impedance testing is superior. Gaseous reflux events associated with small pH drops (>1) have been found with significantly greater frequency in patients with LPR than in those with GERD or in healthy controls. The ability to detect gaseous and mixed (gaseous-liquid) events is particularly important in patients with LPR because gases are more diffusible and can reach higher laryngeal structures. Furthermore, impedance testing detects potentially harmful nonacidic reflux. Pellegrini et al53 called attention to alkaline gastroesophageal reflux long ago, and Galli et al39 demonstrated laryngopharyngeal damage in patients whose gastrectomy procedures resulted in anatomically predictable bile reflux. In a recent report, Sasaki et al55 demonstrated marked inflammatory histological changes in rat laryngeal mucosa exposed to bile salts in both acid and alkaline media; he suggested that biliary and acid reflux may exert a synergistic effect in damaging esophageal mucosa. This finding might also explain some of the therapeutic failures of acid suppression used as the sole treatment for LPR.

Efficacy of PPI Treatment

Unlike with GERD, response to PPI therapy in patients with LPR has been described as highly variable. This is in part because LPR requires more aggressive and prolonged therapy than GERD. Clinical trials have failed to quell the controversy because studies have had different inclusion criteria, failed to stratify populations based on LPR severity, lacked adequate controls, and, often, used inappropriate dosage or duration of therapy. Confounding factors can undermine conclusions; for example, in a class I randomized, placebo-controlled trial designed to demonstrate the efficacy of PPI therapy for LPR, Steward et al57 found that lifestyle modification for 2 months, with or without PPI therapy, significantly improved chronic laryngitis symptoms. In a recent open-labeled, prospective cohort study, Park et al56 shed some light on the controversy. They concluded that twice-daily dosing of PPI resulted in significantly higher symptom relief than daily dosing (P = .03) and noted that nonresponders improved when twice-daily dosing was extended from 2 to 4 months. Like Fackler et al,32 they found that the addition of H2-antagonist therapy at bedtime was of no added benefit. Further clarification is anticipated based on the Cochrane Database of Systematic Reviews protocol that will focus on clinical trials with attention to randomization, selection bias, blinding process, and outcome assessment in reviewingacid reflux treatment of hoarseness.

REFERENCES


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