Introduction

Laryngopharyngeal reflux disease (LPRD) was first described in the 1960’s, but did not come into the forefront of otolaryngology practice until Koufman’s landmark thesis on the subject in 1991. Since that time, from 1990 to 2001, reflux related visits to otolaryngology practices increased >300% and prescriptions for proton pump inhibitors (PPIs) increased 14-fold. Today in otolaryngology practice, we daily see patients who present with hoarseness, dysphagia, globus, chronic throat clearing, and/or cough. The typical management is algorithm is laryngoscopy is performed revealing non-specific findings, a tentative diagnosis of LPRD is made, and PPI therapy is initiated for a 2-3 month trial. However, about half of these patients return with persistent symptoms. So the question that faces us now is how can we improve our approach to patients with LPRD-type symptoms to achieve better, more successful outcomes?

The pathophysiology, diagnosis, and management of LPRD all present challenges to the clinician. The pathophysiology is not fully understood, and several new mechanisms have been proposed within the last few years. The diagnosis of LPRD is based on non-specific, wide-ranging symptoms and non-specific laryngoscopy findings, which leads to confusion of LPRD with other disorders. The co-existence of LPRD with other disorders further confounds diagnostic efforts. Clinicians seeking guidance from the literature on the management of LPRD find that there is no definite standard of management, and there is conflicting evidence and high failure rates even with the most accepted management protocols. We will explore these three main areas further and present a review of the latest literature pertaining to each.

Pathophysiology

The traditional mechanism of LPRD is retrograde flow of gastric acid and pepsin, which leads to laryngeal mucosal damage and impaired mucociliary clearance. While up to 50 reflux events per day is normal and tolerated in the distal esophagus, as few as 3 reflux events per week touching the larynx can injure the vocal fold mucosa. The four barriers to reflux are the lower esophageal sphincter (LES, most important of the four), the upper esophageal sphincter (UES), esophageal peristalsis, and gastric emptying. Dysfunction in any of these barriers can lead to pathologic reflux of the esophagus and/or the larynx.
Recently, the role of pepsin in non-acidic reflux has received a great deal of interest. Johnston et al in 2010 found that post-cricoid epithelial cells from patients with symptoms of LPR contained pepsin but those of control subjects did not. Carrying their studies further, they demonstrated that inactivated pepsin at pH 7 is taken into cells by receptor-mediated endocytosis and reactivated, leading to mitochondrial and overall cell damage. The cell damage was prevented by irreversible inactivation of pepsin prior to exposing cells to it, and also by blocking uptake of pepsin into the cells. These findings have created excitement for possible irreversible pepsin inhibitors or pepsin uptake blockers as future adjunctive treatment to current acid suppression therapy.

The heterotopic gastric mucosal patch (HGMP, also known as a cervical inlet patch) has recently been emphasized as a possible source of refractory LPR symptoms in some patients. The HGMP is ectopic gastric mucosa, thought to be congenital, located between the UES and LES. In 2010, Chong and Jalihal reported that 26 (5.6%) of 462 consecutive patients undergoing upper endoscopy during an 18-month period had an HGMP. 73.1% of patients with the HGMP experienced LPR symptoms (chronic cough, hoarseness, globus) versus 25.9% of patients without an HGMP. However, the researchers noted that in most of the HGMP patients, the LPR symptoms were mild and had to be elicited through direct questioning; only 3 of the 26 patients with an HGMP had been referred for LPR symptoms.

**Diagnostic challenges**

The first challenge in making an accurate diagnosis of LPR is the numerous, wide-ranging symptoms that characterize the disease. The symptoms of LPR, in order of frequency from 16 studies are:

<table>
<thead>
<tr>
<th>Hoarseness/dysphonia</th>
<th>Excessive throat mucus</th>
<th>Laryngospasm</th>
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<tbody>
<tr>
<td>Globus sensation</td>
<td>Chronic cough</td>
<td>Asthma exacerbation</td>
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<tr>
<td>Chronic throat clearing</td>
<td>Dysphagia</td>
<td>Loss of upper singing range</td>
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<tr>
<td>Vocal fatigue</td>
<td>Odynophagia</td>
<td>Prolonged warmup time in singers</td>
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<tr>
<td>Voice breaks</td>
<td>Postnasal drip</td>
<td>Heartburn/regurgitation</td>
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<tr>
<td>Sore throat</td>
<td>Halitosis</td>
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<td>Neck pain</td>
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Laryngoscopy should be performed in all patients with LPR; however, the laryngeal findings, like the symptoms, are non-specific. Videostroboscopy is not usually performed in the initial patient evaluation for LPR symptoms, but it plays a critical role in the evaluation of the dysphonic patient. Videostroboscopy has been found to change or modify the diagnosis in 10-47% of adult dysphonic patients with no laryngeal anatomic abnormalities, and was critical for diagnosis in 27-68% of cases.

In an effort to improve diagnostic accuracy in patients suspected to have LPR, Belafsky, Postma, Amin, and Koufman developed the Reflux Symptoms Index (RSI) and Reflux Findings Score (RFS) in 2002. An RSI >13 and an RFS >7 were shown by the authors to be highly predictive of positive pH probe results (please see slides for items on the RSI and RFS).

Twenty-four hour dual pH probe (esophageal and hypopharyngeal probes) monitoring was considered the “gold standard” for the diagnosis of LPR until recently. However, numerous studies have demonstrated relatively poor sensitivity (75-80%), up to a 50% false negative rate, and poor correlation.
with response to PPI therapy.\textsuperscript{1,4,9} Because of these problems and the emerging importance of non-acidic reflux, combined multichannel intraluminal impedance and pH (MII/pH) monitoring has become the preferred technique and closest test to a “gold standard” that we currently have for LPR. MII/pH monitoring can distinguish between liquid, gas, or mixed reflux events, allowing for detection of acid and nonacid reflux and improved diagnostic yield.\textsuperscript{4} The Restech oropharyngeal probe is a newer, minimally invasive pH probe that is well tolerated by most patients. Unlike a standard pH probe, this probe can detect aerosol, and liquid immersion is not required. It has been shown that there is good correlation between the Restech oropharyngeal probe and a standard hypopharyngeal pH probe for measuring duration of acid exposure in the laryngopharynx.\textsuperscript{10} The one drawback is that the probe cannot detect non-acid reflux events; nevertheless, its minimally invasive nature and simple placement make it a valuable diagnostic tool.

**Considering diagnostic alternatives to LPRD**

*Muscle tension dysphonia (MTD)*

Several studies within the last five years have underscored the importance of considering alternate diagnoses when faced with a patient with a presumptive diagnosis of LPR. Cohen and Garrett (2008) retrospectively reviewed charts of 264 new patients referred to the Vanderbilt Voice Center with a primary complaint of persistent hoarseness during a seven-month period.\textsuperscript{3} One hundred forty-eight patients had taken a PPI in 2 months prior to initial evaluation, and these patients were split into two groups. Group 1 (30%) had stopped the PPI due to continued hoarseness and Group 2 (70%) had continued the PPI but had persistent hoarseness and other throat complaints. After a full evaluation, the final diagnoses in these patients were GERD or LPRD (38%), muscle tension dysphonia (30%), vocal fold lesion (30%), vocal fold paralysis (10%), and vocal fold cancer (2%). Voice therapy was the most common therapy for both groups (35% combined), with an improvement demonstrated in 63% who underwent voice therapy. The remaining one hundred sixteen patients of the 264 had not taken a PPI; after a full evaluation and a variety of diagnoses were made, 14.6% of the patients were started on a PPI, and 50% had an improvement; 85.4% were treated with voice therapy, and 78.6% of these patients had improvement. The authors noted that PPIs are likely over-prescribed, and if given to a patient whose underlying disorder is MTD or other non-reflux-related pathology, the PPI is likely to have little or no effect.

Thomas and Zubiaur (2013) performed a retrospective review of 105 patients with voice-related disorders referred to a single practice with a previous diagnosis of LPR over a 3 year period.\textsuperscript{11} Eighty-two (78%) were on PPIs; 23 (22%) were on a non-specified anti-acid treatment. Five percent reported they had had significant improvement in hoarseness after prior treatment; 13% had mild improvement; 79% had no improvement; 3% had worsening symptoms. The final diagnoses for the patients were diverse, but none of the patients were diagnosed with persistent LPR. The most common single diagnosis was MTD, found in 29 (28%) patients.

Van Houtte et al (2011) published a review of the MEDLINE and CENTRAL literature from 1950 through 2009 on muscle tension dysphonia (MTD).\textsuperscript{12} They define MTD as “the pathological condition in which an excessive tension of the (para)laryngeal musculature, caused by a diverse number of etiological factors, leads to a disturbed voice.” Primary MTD is typified by dysphonia in the absence of concurrent organic vocal fold pathology, and is further characterized by excessive, atypical, or abnormal laryngeal
movements during phonation, without obvious psychogenic or neurologic etiology. It occurs primarily in women and accounts for 10-40% of the caseload at a voice center. Secondary MTD is characterized by dysphonia in the presence of an underlying organic condition. Key features in the diagnosis of MTD are a history of vocal misuse, vocal abuse, or stressful life situations; visible or palpable tension around the larynx; and tightness of the paralaryngeal musculature, laryngeal rise, decreased thyrohyoid space, and focal tenderness. On laryngoscopy or stroboscopy, four types of MTD are described. MTD 1 is laryngeal isometric contraction with a posterior open chink because of a hypertonic state of the posterior cricoarytenoid muscle. MTD 2 is supraglottic contraction in which the ventricular folds are adducted to the midline. MTD 3 is anterior-posterior contraction that results in a reduced space between the epiglottis and arytenoids. MTD 4 is extreme anterior-posterior contraction or squeeze. Treatment of MTD begins with patient education on the diagnosis and basic principles of vocal hygiene. Voice therapy is the crux of therapy for MTD; it breaks the cycle of decompensation and overcompensation of the voice. Circumlaryngeal manual therapy (CMT) involves the speech pathologist or the patient applying pressure and massage to sites of focal tenderness and nodularity in the hyoid-laryngeal musculature while the patient hums or sustains vowels. If no improvement within the first two sessions, the patient is unlikely to benefit from CMT. Finally, any underlying organic disorders should be treated as medically or surgically appropriate.

**Allergy**

Another important diagnostic alternative to consider in patients with LPR symptoms is allergy. Randhawa et al (2010) performed a small prospective study on 15 consecutive patients with a primary voice disorder or presenting complaint of a lump in the throat. RSI, RFS, skin prick testing (SPT), and nasal nitric oxide levels were obtained for all patients. LPR was diagnosed if RSI was >13 and the RFS was >10; allergy was diagnosed if both a positive SPT and elevated nasal nitric oxide were obtained. Based on these criteria, 10 (67%) patients were diagnosed with allergy; 3 (20%) were diagnosed with LPR, but were also diagnosed with allergy, and are 3 of the 10 counted allergy patients. 5 (33%) patients were negative on all tests. Although the sample size of the study was small, it emphasizes the importance of considering allergy as a diagnostic alternative for LPR-type symptoms.

Krouse and Altman (2010) published a review in which they describe chronic rhinogenic laryngitis. It is defined as inflammation of the larynx [due to upper or lower airway inflammatory pathology] resulting in related signs and symptoms that last for at least 2 weeks. Symptoms include hoarseness, throat clearing, straining, globus, odynophagia, and cough; there is often with a co-seasonal variation in symptom severity. One proposed mechanism is that pharyngeal dryness and post-nasal drainage can lead to mucosal irritation of the larynx and pharynx, which leads to itching/tickling in the throat, which leads to throat clearing and coughing and resultant laryngeal inflammation. Laryngeal findings characteristic of chronic rhinogenic laryngitis are increased, thick mucus in the endolarynx that can bridge the vocal folds (most specific), mild vocal fold edema, and mild to moderate erythema of the arytenoid mucosa. It should be noted that these findings are all commonly used to diagnose LPR. The authors also discuss inhalational challenge studies that they performed with colleagues at Wayne State University. In these studies, patients with documented allergy to the house dust mite *Dermatophagoides* underwent direct inhalation challenge of the larynx with aerosolized dust mite antigen in increasing
concentrations. With increasing antigen exposure, the patients developed cough, throat clearing, and dyspnea, and post-challenge laryngoscopy revealed development of increased mucus in the larynx compared to pre-challenge laryngoscopy.

**Challenges in the management of LPRD**

Several challenges face the physician who treats patients with LPR symptoms. Both the literature and clinical practice document a highly variable response among patients to PPI therapy, and as many as 50% of patients treated with a PPI for presumed LPRD will return with little or no symptom improvement. In the literature, there is currently a paucity of high quality, randomized, placebo-controlled trials for PPI therapy for LPR. Of the small trials that are available, all show a strong placebo effect, and most show no significant difference in outcomes between PPI and placebo. The great variation in treatment regimens found in the literature further complicates clinical decision-making. Some authors start with BID PPI therapy; while others start with daily therapy. Therapy duration varies from 4 weeks to 4 months. Some advocate using an H2 blocker as adjunctive therapy at night, while others do not. The high variation in treatment response and in treatment strategies raises the specter of overdiagnosis/misdiagnosis of LPRD, and indeed, this has led some authors to even question the existence of LPRD.

Given the wide variety of approaches to LPRD in the literature, Cohen et al (2012) conducted a cross-sectional survey of 1,000 general otolaryngologists to determine (1) the initial treatment approaches to adult dysphonic patients without vocal fold lesions and with normal vocal fold motion, (2) the signs, symptoms, and testing that general otolaryngologists use to assess for MTD and LPR, and (3) what management is undertaken for patients who have failed initial treatment.7 A 27% response rate was obtained. The top three initial treatment approaches (more than one could be chosen) were to refer to speech pathology (63.0%), prescribe a proton pump inhibitor (58.6%), and obtain stroboscopy (57.9%). The top six methods for testing/determining if the patient has reflux were daily PPI (60.8%), laryngeal findings (58.9%), associated throat symptoms (42.4%), twice daily PPI for 1 to 2 months (39.9%), referral to gastroenterology (22.3%), and pH probe study (17.9%). Finally, the top six next steps taken for patients who failed initial treatment were voice therapy (58.2%), stroboscopy (46.9%), referral to a gastroenterologist (43.8%), extend or increase PPI (33.3%), allergy evaluation (31.9%), and referral to a laryngologist (30.8%). This informative study confirms that the variety of diagnostic and treatment approaches present in the literature is reflected in clinical practice.

In 2006, Hopkins et al attempted to perform a Cochrane review on the effectiveness of anti-reflux therapy in patients with hoarseness.15 The authors evaluated all randomized and quasi-randomize, controlled, double-blinded trials available in the literature at the time of the review. Primary measures sought were the proportion of patients with complete and partial resolution of hoarseness and quality of life assessments. A total of 302 studies of hoarseness were identified; only 6 randomized controlled trials were identified, and all compared gastric acid suppression with PPI vs. placebo. None of the 6 studies met inclusion criteria, so no analysis could be performed. It was noted that 4 of the 6 studies showed no significant difference between treatment and placebo arms, and a strong placebo effect was found across all 6 studies.
New developments in the management of LPRD

More recently, two prospective, randomized, double-blinded, placebo-controlled trials have shown a benefit of PPI treatment over placebo for LPR. Reichel et al (2008) compared esomeprazole 20 mg BID vs. placebo. Sixty-two patients with an RSI >13 and RFS >7 were enrolled and 58 completed the study. The RSI and RFS were measured at baseline, 6 weeks, and 3 months. At 6 weeks, the only significant difference between the groups was a decrease in heartburn in the esomeprazole group. At 3 months, a statistically significant decrease from baseline RSI was seen in both treatment and control groups (P <0.001), with a statistically significant greater decrease from baseline observed in the treatment group (P<0.05). There was also a statistically significant greater decrease in the RFS in the treatment group at 3 months, with the greatest difference seen in posterior commissure hypertrophy, followed by erythema and diffuse laryngeal edema. Overall, 78% of patients in the esomeprazole group felt they had complete resolution of symptoms at 3 months vs. 42% in the placebo group (P=0.006).

Lam et al (2010) compared rabeprazole 20 mg BID vs. placebo for 12 weeks. Eighty-six patients with LPR symptoms and RFS >7 were enrolled and 82 completed the study. Interestingly, patients were excluded if allergic causes of laryngitis were identified. All patients were educated on lifestyle modifications. RSI and stroboscopy (with RFS) were performed at baseline, 6 weeks, 12 weeks, and 18 weeks (18 weeks was 6 weeks after discontinuation of treatment). The RSI was significantly reduced at 6 weeks and 12 weeks in the treatment group compared to the control group; at 18 weeks (6 weeks after no therapy in both groups), no significant difference was found between the groups. The RFS was not statistically different between treatment and control groups at 6, 12, or 18 weeks, though at 12 weeks, significance was approached in favor of the treatment group. The authors concluded that their results suggest a longer duration of PPI therapy beyond 12 weeks may be necessary for successful treatment of LPRD.

Expanding research into therapy for LPR beyond anti-reflux medications, Park et al (2012) conducted a concurrent nonrandomized comparative trial investigating the effectiveness of combined voice and medical therapy for LPR vs. medical therapy alone. One hundred patients with LPR (defined by RSI >13 and RFS >7) were split into two groups of 50. The study group received voice therapy for 30 minutes once weekly for 3 months and omeprazole 20 mg BID for 3 months. The control group received only omeprazole 20 mg BID for 3 months. All subjects were evaluated by RSI, RFS, voice handicap index (VHI), and perceptual voice analysis (GRBAS scale) at 1, 2, and 3 months. Significant changes were defined as ≥5 for RSI, ≥3 for RFS, ≥15 for VHI, and ≥1 for GRBAS. Significant changes in each group at 1, 2, and 3 months were as follows:

RSI significant changes (≥5)
- Study group: 42% (1 month), 66% (2 months), 68% (3 months)
- Control grp: 6% (1 month), 16% (2 months), 46% (3 months)

RFS significant changes (≥3)
- Study group: 2% (1 month), 4% (2 months), 50% (3 months)
- Control grp: 0% (1 month), 8% (2 months), 18% (3 months)
VHI significant changes (≥15)
- Study group: 36% (1 month), 40% (2 months), 48% (3 months)
- Control grp: 2% (1 month), 4% (2 months), 20% (3 months)

GRBAS significant changes (≥1)
- Study group: 50% (1 month), 64% (2 months), 72% (3 months)
- Control grp: 6% (1 month), 20% (2 months), 38% (3 months)

The authors concluded that the superior benefits seen in the study group were due to the synergistic effects of the PPI reducing chemical irritation of the larynx and the voice therapy blocking causes of mechanical irritation. Overall, the combination of voice therapy and PPI for LPR patients significantly increased the speed and likelihood of recovery.

On the subject of using an H2 blocker for adjuvant therapy to a PPI, Fackler et al (2002) studied 16 patients with gastroesophageal reflux disease (GERD) confirmed by pH monitoring and 18 healthy controls. All patients received omeprazole 20 mg BID for 2 weeks, then ranitidine 300 mg was added at bedtime for 4 weeks. Acid production was suppressed further from baseline PPI suppression on day 1, but returned to baseline PPI level by 1 month due to tolerance to the ranitidine. Tolerance does not occur with intermittent H2 blocker use, so the authors recommended H2 blocker use on an as-needed basis, such as after a heavy or acidic meal, rather than for daily therapy.

Improving the approach to the patient with LPR-type symptoms

When LPR is considered as a possible diagnosis for a patient, several key items should be obtained from the history. First, is heartburn or a sensation of reflux present? If so, the likelihood of response to PPI therapy is increased. Does the patient have history or symptoms more consistent with allergy, such as a personal or family history of allergic rhinitis or asthma, throat dryness or itching, or a co-seasonal variation in symptom severity? It is important to note that post-nasal drip, if present, can occur with either reflux or allergy, and is therefore non-specific. Does the patient have history or symptoms more consistent with MTD, such as vocal strain, a profession predisposed to vocal abuse/misuse (singers, teachers, preachers, lawyers), or tension or pain involving the paralaryngeal musculature? When examining the patient, one should look for signs of allergy, such as boggy nasal mucosa, inferior turbinate hypertrophy, and cobble-stoning of the posterior pharyngeal wall. Signs of MTD, such as tension or pain on palpation of the paralaryngeal musculature and decreased thyrohyoid space or laryngeal elevation with phonation should be sought. On laryngoscopy, thick endolaryngeal mucus bridging the vocal folds is helpful, in that it suggests a diagnosis of allergy over LPR.

If LPR is the suspected diagnosis after the initial evaluation of the patient, initial treatment should begin with lifestyle modifications: tobacco cessation, weight loss, head of bed elevation, no food intake at least 3 hours prior to recumbence, and avoidance of fatty foods, chocolate, peppermint, tomato-based foods, and alcohol. A three-month trial of a PPI twice a day, 30 minutes prior to morning and evening meals, should be initiated. Strong consideration should also be given to including a 3-month trial of voice therapy, as it may speed resolution of symptoms and improve overall likelihood of symptom resolution. If the initial therapy is successful, one should taper the patient’s PPI; if symptoms recur during tapering, increase the PPI. It should be noted that some patients might require daily PPI therapy indefinitely; if
desired, these patients may be referred for surgical evaluation for fundoplication. If initial therapy fails, the first two steps should be to reassess the patient’s history for alternate diagnoses and to perform or refer the patient for videostroboscopy. If after stroboscopy the diagnosis still remains uncertain, further diagnostic efforts can include 24-hour MII/pH probe or Restech probe monitoring, allergy testing, or upper endoscopy. Finally, if the diagnosis is confirmed to be reflux but medical therapy fails to improve symptoms, consider referring the patient for evaluation for fundoplication.

**Conclusions**

LPRD is a real disease affecting many voice patients, but it is likely over-diagnosed in clinical practice. Strong consideration should be given to alternate diagnoses in the workup of LPR, especially muscle tension dysphonia and allergy. Voice therapy in addition to PPI therapy improves the speed and likelihood of resolution of LPR symptoms. Finally, and perhaps most importantly, videostroboscopy should be performed early for patients diagnosed with LPR who fail initial therapy.
References


