

TITLE: Laryngopharyngeal Reflux With An Emphasis On Diagnostic And Therapeutic Considerations

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Note: missing Table Data can be seen in the .PDF version.

INTRODUCTION

First coined by Kaufman in 1981, laryngopharyngeal reflux (LPR) has also been recognized under other aliases including extraesophageal reflux, reflux laryngitis, and posterior laryngitis. LPR has been postulated to play a role in up to 50% of laryngeal complaints that present in an otolaryngological practice. It has increasingly become an entity that more otolaryngologists are evaluating and treating in their practice. A closer examination reveals that there is a bit of controversy regarding this medical condition stemming from the fact that there are no set diagnostic guidelines, and yet, physicians continue to offer treatment as an established pathological process. The purpose of this writing is to review key characteristics of LPR and to discuss current diagnostic modalities and therapeutic options with a particular acknowledgement of the controversy inherent with them.

PATHOPHYSIOLOGY

LPR refers to the backflow of gastric contents into the larynx, pharynx, and upper aerodigestive tract. In a normal individual, the upper esophageal sphincter (UES) and lower esophageal sphincter (LES) work together to prevent reflux of such contents up the esophagus. Thus, the primary pathological event in LPR revolves around UES dysfunction. Comprised of the cricopharyngeus, thyropharyngeus, and proximal cervical esophagus, the UES attaches to the thyroid and cricoid cartilages and forms a C-shaped sling that wraps around the cervical esophagus with innervation from the pharyngeal plexus, a network of nerves composed of contributions from the superior and recurrent laryngeal nerves, glossopharyngeal nerve, and

sympathetics from the superior cervical ganglion. When the UES allows refluxate to make contact with the laryngopharyngeal segment, the gastric acid and activated pepsin causes direct damage to the laryngeal mucosa. This results in impaired mucociliary clearance, leading to mucus stasis which further exacerbates the mucosal irritation and contributes to patient symptoms such as postnasal drip, throat clearing, and a globus sensation.

UES dysfunction is not the sole etiology behind LPR as some studies have uncovered a biochemical aspect, noting a correlation between LPR and a depletion of the carbonic anhydrase isoenzyme-III (CA-III) in addition to the presence of pepsin in histological analysis of laryngeal tissues affected by LPR. Decreased levels of CA-III, which may be associated with elevated concentrations of pepsin, are important to consider as this condition translates to decreased amounts of bicarbonate anions present to neutralize the acidic nature of gastric contents, and subsequently, there is less chemical buffer to protect laryngeal mucosa.

FEATURES

Individuals with LPR often present with nonspecific complaints, but there is a set of symptoms that physicians have commonly found among this group of patients as listed in Table 1.

Table 1. Key Symptoms of LPR

• Cervical dysphagia	• Globus sensation	• Throat clearing
• Chronic cough	• Hoarseness	• Upright reflux (“daytime reflux”)
• Dysphonia	• Sore throat	

This is not meant to be an exclusive list as LPR may manifest with other symptoms such as asthma exacerbations, otalgia, excessive throat mucus, halitosis, neck pain, odynophagia, postnasal drip, and voice complaints. Such symptoms, however, are also nonspecific and extend along a broad range that can be seen in other medical conditions. Conversely, this same list should not be treated as an inclusive one, either, as not all patients who experience LPR will be afflicted with all of the aforementioned symptoms.

One of the most important aspects to ascertaining whether or not the etiology to a patient's complaints is related to LPR is distinguishing them from symptoms classically experienced in those suffering from gastroesophageal reflux disease (GERD). GERD typically manifests with heartburn, regurgitation, and reflux when laying supine. Consequently, the incidence of esophagitis and Barrett's dysplasia is higher with this condition than with LPR. Dysphagia may also be encountered, but voice and respiratory problems are less common compared to LPR. Otolaryngologists must clearly elucidate these differences to their patients because many of those with LPR may express frustration and denial of their diagnosis because they mistakenly associate the "reflux" aspect of LPR with that found in GERD.

LPR encompasses a myriad of nonspecific physical exam findings specifically revolving around erythema and edema. Hallmark features include interarytenoid erythema and edema, infraglottic edema, and ventricular effacement. The aforementioned interarytenoid changes are often found with similar changes to the posterior commissure, all of which are commonly grouped together under the term, posterior laryngitis. Infraglottic edema may also be known as pseudosulcus vocalis, describing the illusion of what appears to be a second set of vocal folds just inferior to the true vocal folds. As the true and false vocal folds swell in response to refluxate exposure, the clear and distinct borders of the ventricles appear obscured, described as ventricular effacement. Granularity and a cobblestone appearance to the laryngeal mucosa, otherwise known as pachydermia, may also be noted in LPR. Similarly, contact ulcers, granulomas, scarring, and stenosis may also be encountered. It has been shown that the presence of pachydermia alone, however, is not pathomonomic of LPR. On the other hand, contact ulcers and granulomas have been found to be highly indicative of LPR.

There are a number of other medical conditions that LPR has been thought to contribute to, and thus, raises the importance in managing LPR before such potential complications arise. A number of these processes are listed in Table 2.

Table 2. Medical Conditions Associated with LPR

• Asthma	• Granuloma	• Otitis media
• Bronchiectasis	• Laryngeal carcinoma	• Paradoxical vocal-fold motion disorder
• Cervical dysphagia	• Laryngeal papilloma	• Recurrent croup
• Chronic cough	• Laryngomalacia	• Reinke’s edema
• Chronic dysphonia	• Laryngospasm	• Ulceration
• Chronic laryngitis	• Laryngotracheal stenosis	
• Dental caries	• Obstructive sleep apnea	

LPR may present with similar symptoms and related medical sequelae in the pediatric population as in adults, but children may also experience other problems such as feeding difficulties and anorexia, nasal obstruction or rhinorrhea, otitis media, recurrent upper respiratory infections, sleeping disorders, and subglottic stenosis. There are a variety of other pathologies affiliated with pediatric LPR, but that is beyond the scope of this text.

DIAGNOSTICS

At the time of this writing, there are no set guidelines for a definitive diagnosis of LPR. Much of the literature considers ambulatory 24-hour double-probe pH monitoring as the current diagnostic standard. This study entails measuring the pH in the proximal and distal esophageal

regions. A positive event is defined as a pH-drop in the proximal probe accompanied by a simultaneous decrease in the distal one. Although there does not appear to be a significant difference in results between sedated and unsedated individuals, dual-probe pH studies are susceptible to false positives that require manual correction.

Impedence studies are one developing technological advance that expands on the principles behind pH monitoring. This technique involves arranging multiple electrode pairs on a pH-probe-type catheter capable of tracking retrograde bolus transits suggestive of reflux. Some physicians advocate impedance studies over pH monitoring due to its ability to measure acidic and nonacidic events as opposed to the sole detection of acidic events that dual-probe pH monitoring provides.

Such studies are considered invasive, costly, and uncomfortable, and they are not available to all institutions. In an attempt to provide a simpler, validated objective diagnostic tool, Belafsky *et al* (2001) developed the Reflux Finding Score (RFS). The RFS serves as a scoring tool that grades eight specific physical exam findings that may be attributed to LPR. Some of the components are scored as whether or not they are present while others are graded in regards to its severity. The RFS can range from 0 to 26, and the authors concluded that a score greater than 7 suggested a 95% statistical likelihood of a positive dual-probe pH study. This is also applicable for asymptomatic patients. The components of the RFS are depicted in Figure 1.

- **Infraglottic edema (pseudosulcus vocalis)**
0 (absent) 2 (present)
- **Ventricular obliteration**
0 (none) 2 (partial) 4 (complete)
- **Erythema/hyperemia**
0 (none) 2 (arytenoids) 4 (diffuse)
- **Vocal fold edema**
0 (none) 1 (mild) 2 (moderate) 3 (severe) 4 (polypoid)
- **Diffuse laryngeal edema**
0 (none) 1 (mild) 2 (moderate) 3 (severe) 4 (obstruct)
- **Posterior commissure hypertrophy**
0 (none) 1 (mild) 2 (moderate) 3 (severe) 4 (obstruct)
- **Granuloma or granulation**
0 (absent) 2 (present)
- **Thick endolaryngeal mucus**
0 (absent) 2 (present)

Figure 1. RFS Components

To supplement the diagnostic value of the RFS, Belafsky *et al* (2002) developed the Reflux Symptom Index (RSI). The RSI was created with the intention to serve as a validated self-administered 9-question survey administered to patients who graded specific symptoms on a scale from 0 to 5. Similar to the RFS, a RSI score greater than 13 was found to suggest a positive dual-probe pH study. In addition, the authors had noted that RSI scores tended to

decrease before actual physical exam improvements were noted with effective medical management. A depiction of the RSI is presented in Figure 2.

Within the last MONTH, how did 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					

Figure 2. RSI

The RFS and RSI are not the sole clinical diagnostic tools available to evaluating LPR. Beaver *et al* (2003) had engendered a scoring system similar in nature to the RFS with the Laryngopharyngeal Reflux Disease Index (LPRDI) to be used in conjunction with videostroboscopy. Out of twelve specific physical exam findings, the LPRDI was found to be more useful in assessing for LPR with regards to erythema and edema of the supraglottic, glottic, and subglottic regions. Other criteria such as leukoplakia, nodules, polyps, posterior pachydermia, webs, and contact granulomas were not found to be as reliable.

There are other tests that have been suggested as helpful in evaluating LPR. Studies on them are small, and consequently, are not routinely recommended as part of the initial workup. These options are listed in Table 3.

Table 3. Additional Diagnostic Tools

• Acidification tests	• Esophagram	• Mucosal biopsy
• Bronchoalveolar lavage	• Flexible endoscopic evaluation of swallowing	• Reflux scan
• Esophagogastro-duodenoscopy	• Manometry	• Refluxate analysis
		• Voice analysis

Mucosal biopsies have been notable for its ability to measure the concentration of pepsin and CA-III. A pepsin immunoassay being developed has been postulated to be 100% sensitive and 89% specific for LPR (Knight *et al*, 2005). Spectrophotometric analysis of refluxate has garnered attention for its potential to evaluate for bile and pancreatic enzymes, two biochemical

compounds that may possibly aggravate the laryngeal mucosal damage incited with LPR in addition to gastric acid and activated pepsin.

TREATMENT

Treatment options for LPR can be divided into three main modalities: lifestyle modifications, pharmacological, and surgical. Lifestyle modifications are similar to changes suggested for individuals experiencing GERD. Patients should be instructed to avoid oral intake 2-3 hours prior to lying supine and to elevate the head of the bed. Elevation should be undertaken with the placement of bed blocks as opposed to the use of additional pillows. In addition, patients are encouraged to sleep on their left side as the diaphragmatic crura is said to cause a natural kink in the gastroesophageal junction when a person is in the left lateral decubitus position. Weight loss is usually helpful if symptoms of both LPR and GERD are present. Patients are educated to avoid alcohol, caffeine, carbonated beverages, chocolate, tobacco, and foods that are fried, spicy, or contain citrus as these factors have been noted to exacerbate reflux.

Antacids and histamine-2 receptor antagonists (H2RA) were the mainstays of pharmacological therapy prior to the development of proton pump inhibitors (PPI) in the 1980's. Aside from the symptomatic relief that antacids afford against the acidic component of gastric refluxate, H2RA's were prescribed to combat a histamine-regulated nocturnal acid breakthrough (NAB) that is felt to further exacerbate symptoms due to LPR. Early studies had concluded that the combination of H2RA and PPI therapy effectively controlled NAB only during the initial part of treatment (Fackler *et al*, 2002), while later ones had suggested that there was an equivocal difference with the addition of H2RA to an established twice-daily PPI regimen (Ours *et al*, 2003).

PPI's are currently considered the cornerstone to pharmacological treatment of LPR. Its optimal effect exerted when taken 30-60 minutes prior to meals, PPI's reduce gastric acid production by blocking the gastric proton pump. While establishing the RFS and RSI, Belafsky *et al* (2001) had observed that significant physical exam improvements were noticeable after four months of twice-daily PPI therapy. Other placebo-controlled studies have produced results that support the potential benefit garnered with long-term PPI use. Despite a placebo-effect noted early in the course of treatment, Reichel *et al* (2008) revealed improvement to laryngeal symptoms and appearance with twice-daily esomeprazole. In a similar manner, Noordzij *et al* (2001), El-Serag *et al* (2001), and Steward *et al* (2004) concluded that PPI therapy led to noticeable symptomatic relief even if associated physical exam signs were not as apparent. Furthermore, Wo *et al* (2006) reiterated the superiority of a twice-daily regimen over a once-daily one.

Performing a Nissen fundoplication is the primary surgical option pursued if medical management does not alleviate LPR in patients. Entailing the encirclement of the esophagus with the gastric fundus, fundoplication carries a 90% ten-year success rate in those experiencing GERD. Available literature suggests a Nissen fundoplication may improve LPR-related signs and symptoms in 73-86%, although it should be noted that there appears to be a poorer response to surgery in those who have failed four months of medical therapy--and yet, surgery is an option offered to those who do not exhibit significant improvement under such conservative management.

The accepted treatment protocol revolves around empirically treating suspected LPR, based on an appropriate history and physical along with associated elevated RSI and RFS scores, via a combination of lifestyle modifications and twice-daily PPI with or without supplemental H2RA's. Follow-up is suggested after at least three months to assess for clinical changes. If patients report resolution to their symptoms, the medications are typically weaned although typically less than 10% of them will successfully remain asymptomatic after complete discontinuation. For a partial symptomatic response, an increase in the PPI dose is recommended followed by further assessment of interval improvement in another three months. Some otolaryngologists, on the other hand, may prefer to start empiric treatment with the maximum dose in the first place and forego this step. A poor response or even worsening of symptoms prompts the need to perform a more in-depth evaluation with ruling out other medical conditions that may manifest with similar symptoms and conducting more invasive diagnostic tests including pH or impedance monitoring and esophagogastroduodenoscopy. Figure 3 outlines this treatment algorithm.

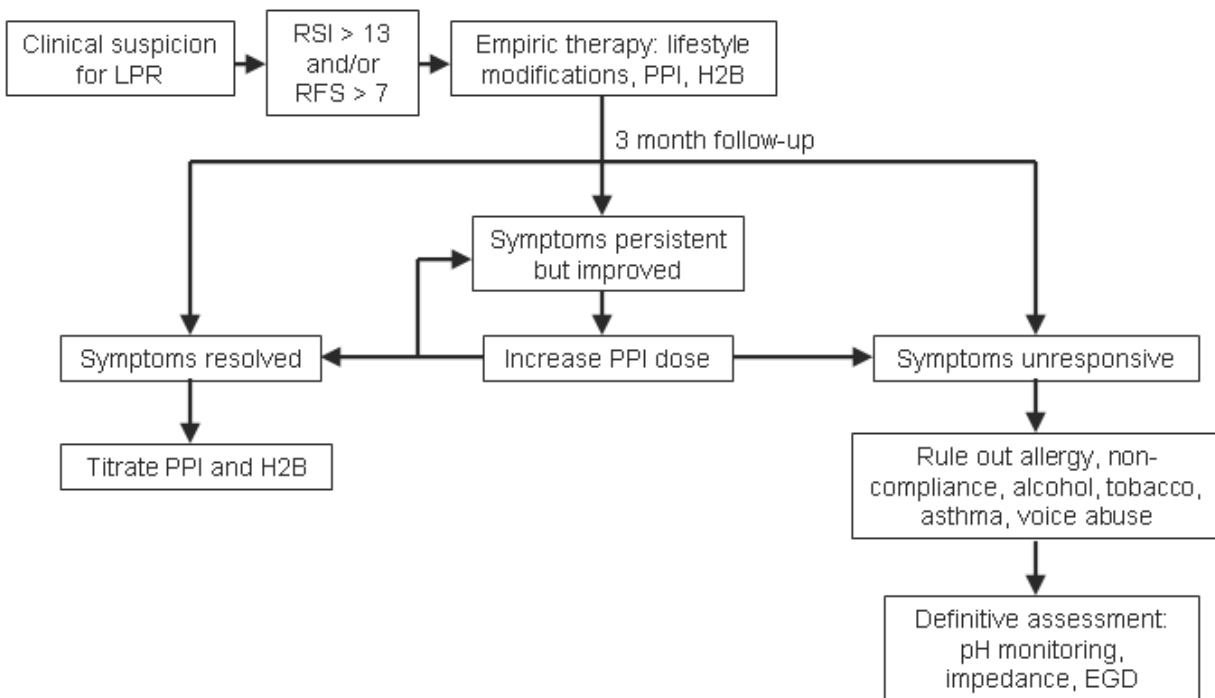


Figure 3. Treatment Algorithm

CONTROVERSY

The nonspecific nature of symptoms and the lack of set criteria for diagnosis leaves LPR susceptible to a couple of foci of controversy. Although there are hallmark findings and symptoms associated with LPR, not all patients will present with these complaints nor exhibit all of the classic features. Consequently, these patients may be erroneously evaluated for allergies, asthma, sinusitis, smoking, and vocal abuse. In addition, up to 87% of healthy individuals have been noted to have at least one LPR physical exam finding despite remaining asymptomatic. Conversely, Ylitalo *et al* (2001) had shown that some people possessed a benign laryngeal examination despite complaints indicative of reflux. Further compounding the problem posed by

the absence of diagnostic guidelines, there is a poor level of inter-rater reliability which leads to a subjective diagnosis of LPR.

Despite currently being regarded as the gold-standard in diagnosing LPR, pH monitoring is not without its caveats. Positive pH studies have been recorded in approximately 70% of patients who presented with signs and symptoms commonly encountered in LPR, and thus, implying that a negative pH study does not definitively rule out LPR. In a similar manner, LPR events recorded on pH monitoring have been demonstrated in up to 30% of asymptomatic individuals, albeit at significantly shorter acid exposure times compared to symptomatic patients.

Finally, there has been debate regarding the optimal placement of the proximal pH probe. This probe has classically been positioned past the UES with a positive result defined as a pH drop to 4. Some physicians advocate placing the probe in the hypopharynx, maintaining that this location provides a more direct measurement of the laryngopharyngeal segment with a positive finding defined as a pH drop to 5. This assertion is countered with the argument that this position leaves the proximal probe susceptible to false-positives secondary to any drying that may occur as opposed to the moister environment of the proximal esophagus.

CONCLUSION

There is currently enough evidence to acknowledge a relationship between LPR and laryngeal symptoms, if not necessarily causality. It is important to both the otolaryngologist and the patient to distinguish this condition as a separate entity apart from GERD although definitive diagnostic criteria have not yet been established. While with its inherent flaws, definitive diagnostic testing is expensive, invasive, and not available at all institutions. Once LPR is suspected, the mainstay of therapy involves empirically treating with appropriate lifestyle modifications and twice-daily PPI followed by reassessing for symptomatic improvement.

Discussant's Remarks: Dr. Michael Underbrink:

This was a good discussion on LPR, and there's a lot of controversial data in the literature, especially noticing the population of patients that I see with nonspecific laryngeal complaints that don't seem to fit into any category except LPR.

The concepts that I use in my practice when addressing LPR are the use of the RFI and RFS. Remember, the RFS is pretty specific to videostroboscopy findings.

Sometimes you see some infraglottic edema or posterior commissure hypertrophy, and immediately diagnose LPR. There are some experts in the field that believe that posterior commissure hypertrophy is a normal or non-specific finding on laryngoscopy.

There was a recent study by a Gastroenterologist from the Mayo Clinic examining random people off the street without any symptoms of LPR, and over 50% were found to have a finding of posterior commissure hypertrophy.

This finding may be useful, however if combined with other signs of LPR, such as erythema and edema

For the RSI (Reflux Symptom Index), I give a questionnaire to the patient that has been validated to correlate well with a positive pH probe, when scored above 13.

If I see three or more laryngeal findings with a positive RSI, I go ahead and start them on b.i.d. PPI therapy for three months and then reassess the patient.

If they're not improved by three months I think it's time to get a gastroenterologist involved and investigate further, using impedance testing, or formal pH probe testing.

Remember, sometimes patients are not compliant or can't afford the medication.

My own experience is that most people with symptoms, who do improve after three months of therapy, are very happy with the costs of this treatment regimen.

If you distill all the literature out there I think there's certainly a place for empiric therapy for significant signs and symptoms of LPR.

This was a very good talk. Thank you, Dr. Pham.

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