Chapter

Updates on Laryngo-Pharyngeal Reflux (LPR) and Its Management

Hardip Singh Gendeh and Balwant Singh Gendeh

Abstract

Laryngo-pharyngeal reflux (LPR); esophageal reflux; pharyngolaryngeal reflux; or reflux laryngitis refers to the backflow of acid from the stomach to the upper aerodigestive tract of the larynx and pharynx. Repetitive reflux of these contents may lead to LPR. It has been estimated that half of the otolaryngology patients with laryngeal and voice disorders have LPR. The pattern of reflux is different in LPR and gastroesophageal reflux. LPR usually occurs during the daytime in the upright position, whereas gastroesophageal reflux disease more often occurs in the supine position at nighttime or during sleep. Laryngeal edema is an important indicator of LPR that is most often neglected. LPR was previously deemed a controversial topic in laryngology but is now clearer with a better understanding of the pathogenesis. Diagnosis is made based on symptoms, and laryngoscopy aided with investigations and confirmed the response to treatment.

Keywords: laryngo-pharyngeal reflux, esopharyngeal reflux, pharyngolaryngeal reflux, reflux laryngitis, management, updates

1. Introduction

Laryngo-pharyngeal reflux (LPR); esopharyngeal reflux; pharyngolaryngeal reflux; or reflux laryngitis refers to the backflow of acid from the stomach to the upper aerodigestive tract of the larynx and pharynx. The larynx has a neutral ph of 7 compared to the acidity of the stomach at ph 1.5 to 2. As a result, whenever stomach contents encounter the larynx, the laryngeal trauma caused by reflux contents often consist of digestive enzymes, such as pepsin, bile salts, and pancreatic enzymes. Repetitive reflux of these contents may lead to LPR [1].

Gasto-esophageal reflux disease (GERD) on the other hand refers to the retrograde flow of gastric contents into the esophagus. Cherry et al. (1968) first suggested LPR being caused by GERD in three patients with persistent contact ulcers of the larynx, having shown reflux peptic esophagitis. These patients had reflux from the esophagus to the pharynx *via* the cricopharyngeal when studied using a barium swallow. Although they did not present with symptoms of GERD, further assessment and history revealed the possibilities of GERD [2].

There is still a debate about whether LPR is a subset of GERD because naturally for LPR to be present, gastric contents will first have to reflux into the esophagus prior to reaching the pharynx and larynx superiorly. Some have argued that GERD

and LPR are separate entities as some reflux into the esophagus may occur and the esophagus is more forgiving to the acidic contents of the stomach as compared to the pharynx and larynx. A patient with reflux may have symptoms of LPR but not GERD. On the contrary, patients with significant GERD without typical symptoms of GERD may present as LPR. These are the cohort of patients who will present to the Otorhinolaryngology specialty for laryngeal symptoms instead. Fraser et al. (1994) have suggested that then laryngeal symptoms (primarily hoarseness) now known as LPR were symptoms of GERD rather than LPR alone. Upon treatment with proton pump inhibitors, these patients report improvements in GERD but not LPR [3].

Some authors have suggested that LPR is not GERD and *vice versa*. Therefore, this chapter explores the causation, symptoms, examination findings, and treatment of LPR and why it does exist.

2. Cause and pathophysiology

Two mechanisms have been proposed for causing LPR [3]. They are as follows:

1. **Gastric reflux at the lower esophagus stimulates a vagal reflex.** This leads to coughing and throat clearing, eventually leading to laryngeal symptoms. Therefore, in this theory, there is no direct insult to the laryngeal mucosa by peptic acid contents.

2. **Gastric reflux bypasses the upper esophageal sphincter causing a direct insult to the laryngeal mucosa.** This has been difficult to prove as pH studies involving a pharyngeal problem have been challenging.

Based on the Montreal Criteria, LPR is defined as the reflux of gastric contents into the esophagus, resulting in symptoms and complications, such as esophagitis, which may develop into a Barrett's esophagus [4]. A patient with LPR may be asymptomatic of GERD symptoms and may fail to meet the diagnostic criteria of GERD. It is estimated that up to 44% of patients with LPR may have a normal esophagogastroduodenoscopy (OGDS) [5, 6]. Therefore, this suggests that LPR and GERD are two separate diagnostic entities, and one may occur independently without the other [7].

Lechien et al. (2020) have highlighted gray areas in the pathophysiology of LPR. Among them is the role of bile salts, which have been shown to be the route of a reflux content causing inflammation to the laryngopharynx. Gastric reflux may contain bile. Little has been done to investigate this among humans. The use of prolonged proton pump inhibitors has been shown to alter the pharyngeal microbial flora, another factor that needs to be investigated as a causative factor. Wang et al. (2019) found a significant correlation between autonomic nerve dysfunction among 81 patients with suspected LPR. There was no correlation between vagal dysfunction and LPR [8]. Stress may upregulate sympathetic nervous system activity, therefore altering the autonomic nervous system and resulting in LPR. Sympathetic activity is believed to be a known cause of a transient relaxation of esophageal sphincters [9].

Patients with LPR are said to have less carbonic anhydrase enzyme, which secretes bicarbonate [10–12], resulting in less bicarbonate content, which is an alkali to neutralize the refluxed gastric contents. Acidity plays an important role. The gastric mucosa has a pH of 1.5 to 2.0, while that of the laryngopharynx is neutral. As little as three episodes of reflux of gastric contents in a week to the laryngopharynx decreases

its pH to a more acidic environment, thus traumatizing the laryngopharynx [11, 12]. The pH of 4.0 is sufficient to traumatize the larynx [13].

Some authors have postulated the role of nonacid reflux, whereby other gastric contents, such as pepsin, are the contributing factor [11, 14]. Symptomatic patients have been shown to have nonacid reflux in a week *via* impedance monitoring. Pepsin may have refluxed and deposited at the laryngopharynx, which is neutral. The presence of acid *via* hydrogen ions from another episode of acid reflux or diet then activates the pepsin enzyme, resulting in intracellular damage [14].

It has been estimated that half of the otolaryngology patients with laryngeal and voice disorders have LPR [15]. The pattern of reflux in LPR and gastroesophageal reflux may vary. LPR usually occurs during the daytime in the upright position, whereas gastroesophageal reflux disease more often occurs in the supine position at nighttime or during sleep. Laryngeal edema is an important indicator of LPR that is most often neglected. Ambulatory 24-h double pH-probe monitoring is the gold standard diagnostic tool for LPR. Besides, gastric mucosa, and laryngeal H pylori have been shown to precipitate GERD. 57% of LPR patients have H pylori. Laryngeal acid and pepsin sensitivity are greater in oropharyngeal mucosa than in esophageal mucosa and this constitutes the main difference between LPR and GERD pathophysiology. *H. Pylori* is found in many sites, including laryngeal mucosa and inter-arytenoid region; however, the importance of this colonization and its effects on disease progress and treatment outcome is yet to be identified with prospective clinical studies [16].

Obesity, smoking, and alcoholic lifestyle changes are contributing factors to GERD, LPR, or both. Smoking and alcohol may result in the worsening of GERD or cause direct trauma to the laryngeal mucosa, thus increasing the severity of LPR symptoms. Obesity simply increases intra-abdominal pressure, increasing the likelihood of GERD or silent GERD.

3. Symptoms

Koufman studied the severity of laryngeal injury in 250 patients with suspected GERD with 24-hours ambulatory esophageal monitoring. In total 197 (81%) of patients had double monitoring with the second probe being placed at the laryngeal inlet at the laryngopharynx. Sixty-one patients had reflux laryngitis. The study revealed that the commonest laryngeal symptoms of patients with suspected GERD were hoarseness, cough, globus sensation, and frequent throat clearing, indicating a possible silent GERD. Among them, only 43% had GERD symptoms of heartburn or acid regurgitation. This differentiates LPR from GERD, whereby heartburn and acid regurgitation are GERD-specific.

Other less specific symptoms are persistent sore throat, excessive laryngeal mucus, dysphagia, and halitosis [17]. The significant LPR has been associated with rhinology symptoms, where the severe reflux content reaches the nasopharynx, thus irritating the nasal mucosa. Pepsin has been found within the epithelium of the inferior turbinate's glandular mucosa and nasal secretions among patients with chronic rhinosinusitis with or without nasal polyposis [18]. A thorough history is indicated to identify a postnasal drip, causing laryngeal irritation and chronic cough among patients with rhinitis symptoms. Nasal endoscopy is often beneficial to ascertain the presence of posterior choanal secretions. LPR may manifest as other laryngology diagnoses, such as subglottic stenosis and laryngeal malignancy. Muscle tension dysphonia and laryngeal spasms may occur too [19].

Hoarseness
Frequent throat clearing
Globus pharyngeus
Chronic cough

Table 1.
Common symptoms of LPR.

Hoarseness can be caused by a variety of laryngeal pathology. It is predominant in LPR patients and should be considered in patients with hoarseness for more than 3 months [17]. LPR or GERD associated hoarseness is a change in voice that tends to occur upon waking up and improves with the day. It was initially thought that a supine position during sleeping encourages gastric reflux into the larynx, resulting in hoarseness, which shall improve upon resuming an upright position. However, Ozturk et al. (2006) have proven that most patients recorded LPR in the upright position as opposed to supine [17, 20]. Koufman et al. have shown that LPR patients have daytime refluxes [13]. Throat clearing can be abusive to the larynx, causing further trauma. Globus pharyngeus is the feeling of a lump in the throat akin to a foreign body sensation. This is unlike odynophagia, which is pain on swallowing. Laryngeal irritation may lead to a cough.

There has been great debate on what is an acceptable LPR episode. A range of 1–4 LPR episodes a day has been given to cause symptomatic LPR [17]. Healthy and asymptomatic individuals of LPR are said to have one episode of LPR in a day [17]. The determining factor of LPR symptoms is its severity where symptomatic individuals may present to the primary care physician or Otorhinolaryngology clinic for treatment. Thus, symptomology alone is inadequate for the diagnosis of LPR. The common symptoms of LPR are listed in **Table 1**.

4. Investigations

The above symptoms are nonspecific to LPR and can be associated with many other ENT pathologies and several investigative procedures should be performed to assist in the diagnosis of LPR.

4.1 Laryngoscopy

Laryngoscopy is a must for patients presenting with laryngeal symptoms, which can be performed *via* a rigid or flexible laryngoscopy. Rigid laryngoscopy with 70 degrees Hopkins scope may be uncomfortable but provides a good view of the larynx. Flexible laryngoscopy to a camera head can be performed through the nose known as a flexible nasopharyngolaryngoscope. Newer video laryngoscopy with a camera at the tip of the flexible scope does provide clearer images. Video chromatography has been useful in the diagnosis of LPR [21]. The most common findings among patients with LPR as documented in the reflux finding score (RFS) are [22]:

1. **Posterior commissure hypertrophy:** It is the most common finding in 85% of individuals with LPR. It can be classified into

    a. **Absent:** Cuneiform cartilage is visualized.

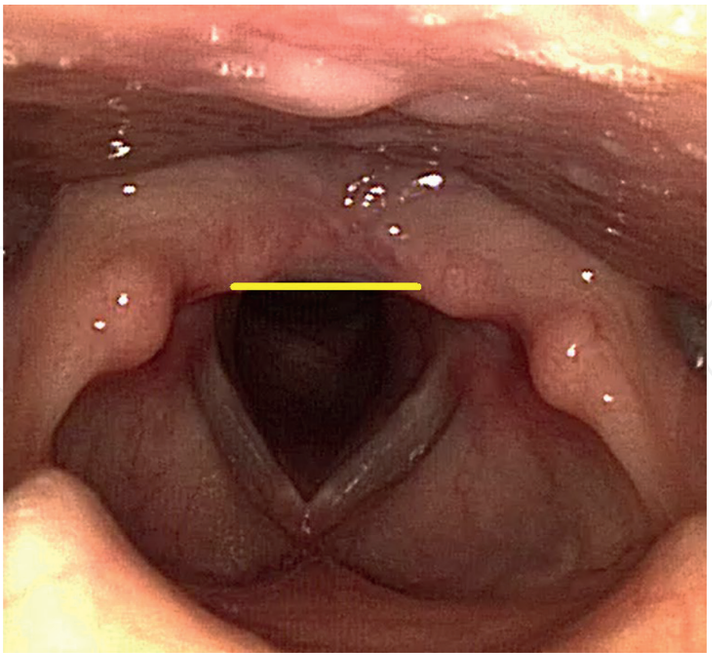

Figure 1.
A moderate posterior commissure hypertrophy with a horizontal line (yellow) at the posterior larynx.

b. **Mild**: Mustache-like appearance of the posterior commissure.

c. **Moderate:** Horizontal line at the posterior larynx (**Figure 1**).

d. **Severe:** More than a horizontal line obliterating part of the posterior segment of the laryngeal inlet.

2. **Ventricular obliteration:** This occurs in 80% of LPR patients. Edema of the true and false cords causes this space to become obliterated; it is further divided into a partial obliteration (whereby the ventricles are partially obliterated with a remaining view of the true cords beneath) and complete obliteration, whereby both the false cord and true cord are edematous, completely obstructing the view of the ventricle in between (**Figure 2**).

3. **Pseudosulcus Vocalis:** Also known as subglottic edema extending from the anterior to the posterior aspect of the larynx and may appear as a double line at the medial free border of the true cords. Pseudosulcus vocalis extends all the way posteriorly throughout the whole length of the vocal fold (**Figure 3**) and it differs from true sulcus vocalis that stops at the midpoint of the vocal fold.

4. **Laryngeal erythema:** Although nonspecific, redness of the larynx can be appreciated, which may be diffuse involving the larynx or confined to the arytenoids. However, this is dependent on image quality, light source, and operator (see **Figure 4**).

5. **Vocal fold edema**: It can be classified into

a. **Mild:** Slight edema

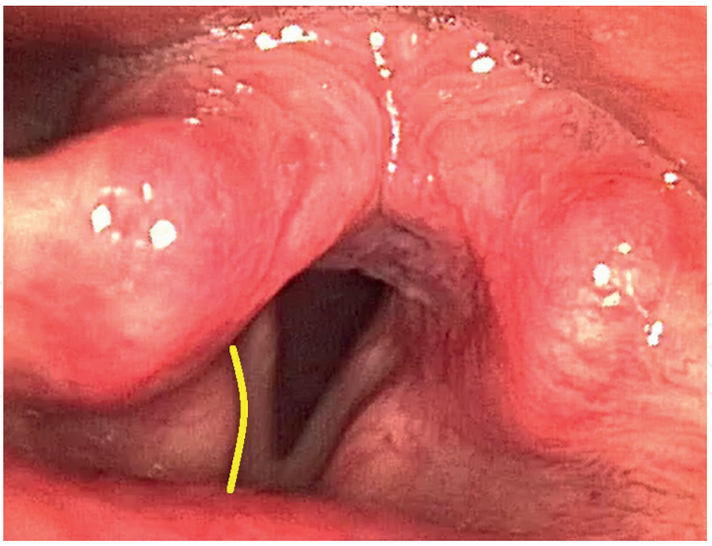

Figure 2.
Edematous false and true cords with partial obliteration of the ventricles (yellow line). There is also bilateral arytenoid erythema.

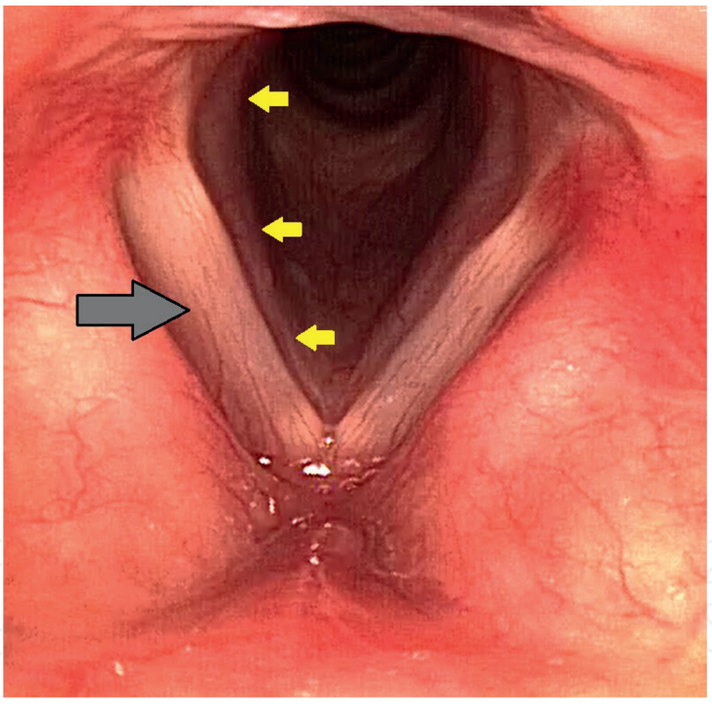

Figure 3.
Pseudosulcus extending posterior (yellow arrows) throughout the length of the true cord (gray). The same appears on the contralateral side.

b. **Moderate:** More perceptible than mild.

c. **Severe:** Edema is appreciated as a sessile swelling involving the whole vocal fold.

d. **Polypoidal**: More than severe that gives rise to a bulky polypoidal appearance.

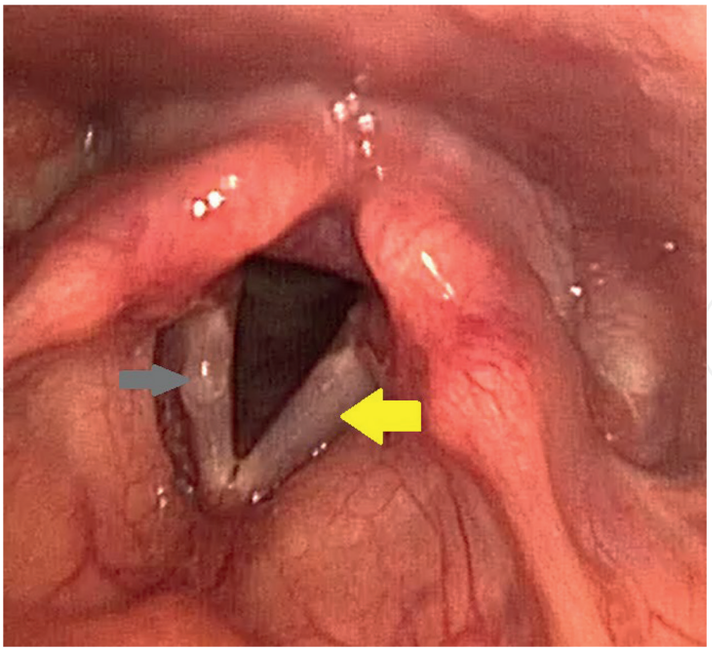

Figure 4.
Edema of the true cords (yellow arrow) bilaterally with thick endolaryngeal mucus at the right midsection of the true cord (gray arrow). The secretions disappeared upon asking the patient to cough.

6. **Diffuse laryngeal edema:** The size of the airway is compared relative to the size of the larynx and is classified into mild; moderate; and severe obstruction. The authors find this classification vague and subject to the interpretation of the operator (**Figure 5a, b**). The above 1–5 scores may contribute to diffuse laryngeal edema.

7. **Granulation tissue:** Granuloma may be present anywhere within the larynx (**Figure 6**).

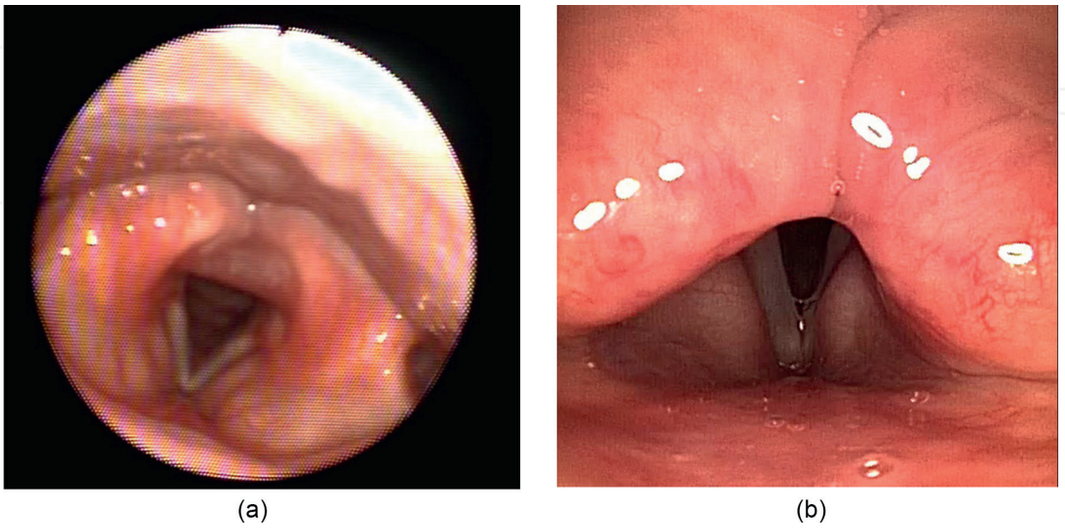

Figure 5.
a: Appreciate the diffuse edema of the supraglottic and glottis structures. There is also ventricular obliteration and posterior commissure hypertrophy. b: Diffuse laryngeal edema, ventricular obliteration, thick endolaryngeal mucus, and supraglottic squeeze during vocalization. As a result, the true cords are partially visualized.

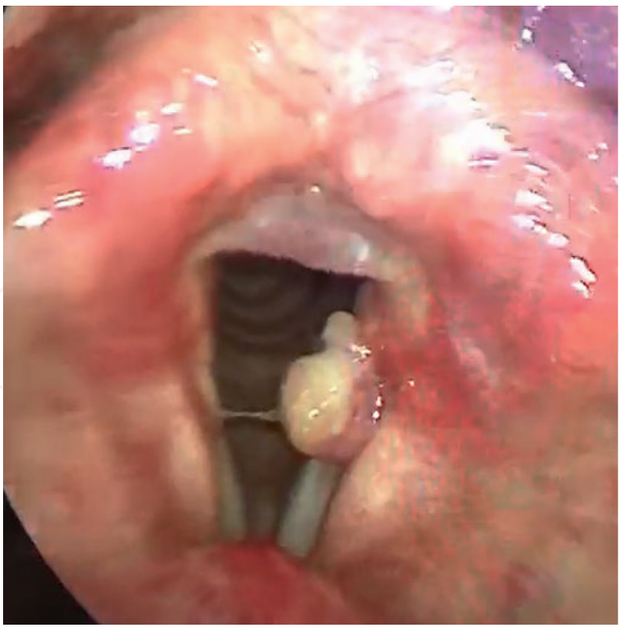

Figure 6.
Granulation tissue from the left true cords in a patient with dysphonia. There is severe posterior commissure hypertrophy extending into the airway. Also, bilateral ventricular obliteration. The patient was a singer and had significant symptoms of LPR.

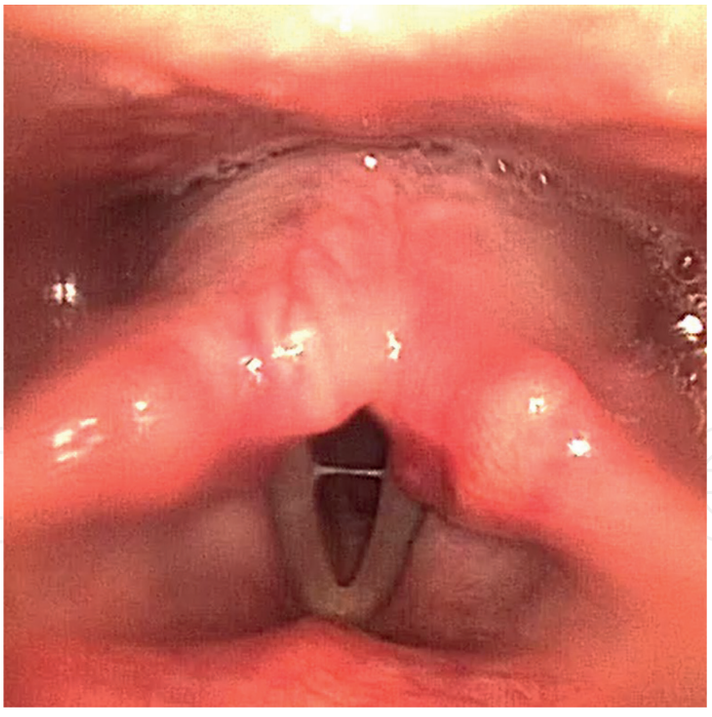

Figure 7.
Thick endolaryngeal mucus across the posterior third of the true cords. There is also edema of the true cords.

8. **Thick endolaryngeal mucus:** This can be appreciated as a horizontal mucus line across the larynx or thick clear secretions within the larynx (**Figure 7**).

Laryngoscopy is a good opportunity to rule out other hypopharyngeal and laryngeal causes of LPR symptoms. It is important to examine the nasal passageway *via* nasal endoscopy. Look out for signs of rhinitis and secretions within the postnasal choana,

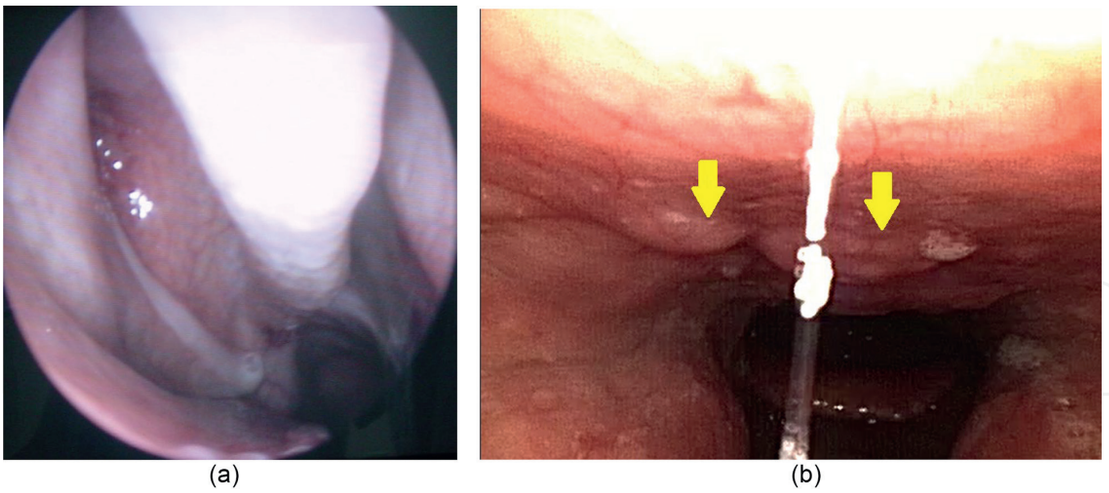

Figure 8.
a: Nasal endoscopic view of the right nose showing mucopurulent discharge from the maxillary ostium draining into the nasopharynx as a postnasal drip (PND). b: FNPLS of the posterior pharyngeal wall (arrows) from the nasopharynx overlooking the oropharynx inferiorly. Appreciate the secretions at the nasopharynx and granular posterior pharyngeal wall. The patients should be examined for rhinitis and a postnasal drip.

which may contribute to posterior nasal drips, resulting in frequent throat clearing and mimicking signs of LPR. They may be concomitant rhinitis with significant postnasal drip and LPR, where rhinitis also needs to be managed (**Figure 8a, b**).

4.2 Esophageal pH monitoring

Esophageal monitoring with a pH probe is the gold standard for identifying gastric acid reflux. LPR is confirmed when pH at the distal esophageal sphincter is less than four for more than 24 hours [20]. A distal esophageal probe is often placed 5 cm above the lower esophageal sphincter to allow for swallowing and prevent displacement into the stomach. Multichannel intraluminal pH monitoring is useful in detecting both acid and nonacid reflux. As, yet, there has been no absolute agreement on pH value that is acceptable to diagnose LPR. There has also been a debate on where to apply the probe for proximal pH monitoring at the hypopharynx, where a fixed double sensor probe is positioned at the hypopharynx will cause an inaccurate position in the distal esophagus and *vice versa* [23]. A dry proximal probe or ingestion of acidic food may result in a pseudo reflux. On the contrary, the reliability of an upper probe in diagnosing LPR is questionable. The presence of acid distal to the upper esophageal sphincter may not represent the same scenario proximal to it within the hypopharynx as the proximal esophageal sphincter itself acts as a barrier to gastric reflux [23]. Some authors have suggested the use of a triple sensor; first proximal; second distal to the upper esophageal sphincter; and third proximal to the lower esophageal sphincter [23]. It has been difficult to correlate the reflux severity and the intensity of LPR [11, 20].

4.3 Reflux symptoms index

The Reflux Symptoms Index (RSI) is a self-administered nine-item outcome for the diagnosis of LPR, which can be completed in less than 1 minute during a consultation. It has a maximum total score of 45 with each nine questions ranging from 0 (no symptoms) to 5 (severe symptoms). It has been validated and shown to be reproducible when compared with Voice Handicap Index (VHI) pre and 6 months posttreatment among patients with LPR [24]. Those with 5 points or more improvements in

Within the last month, how did the following problems affect you?	0 = no problem					
Circle the appropriate response.	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 mucus or postnasal chip	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.Breadline 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			

Table 2.
Reflux symptoms index (RSI).

Subglottic edema	0 = absent 2 = present
Ventricular	2 = partial 4 = complete
Erythema/hyperemia	2 = arytenoids only 4 = diffuse
Vocal fold edema	1 = mild 2 = moderate 3 = severe 4 = polypoid
Diffuse laryngeal edema	1 = mild 2 = moderate 3 = severe 4 = obstructing
Posterior commissure hypertrophy	1 = mild 2 = moderate 3 = severe 4 = obstructing
Granuloma/granulation tissue	0 = absent 2 = present
Thick endolaryngeal mucus	0 = absent 2 = present

Table 3.
Reflux finding score (RFS) [22].

RSI correspond to a likely 11 points improvement with VHI [24]. Since normal healthy individuals may have reflux too, a score of >13 is considered abnormal. Its limitations include failure of representation of symptoms frequency and others, such as throat pain, odynophagia, and halitosis [7]. **Table 2** illustrates the RSI questionnaire.

4.4 Reflux finding score

The Reflux Finding Score (RFS) was diagnosed to represent the physical manifestations of LPR evident during a fiberoptic laryngoscopy, which consists of eight items of the commonest laryngeal findings seen during LPR with a maximum score of 26. The mean RFS for LPR patients pretreatment was 11.5 with a significant trend of improvement to 6.1 at 6 months upon initiating treatment [22]. It is used as a tool for the standardization of findings among clinicians for assessment, treatment follow-up, and efficacy. A score of >7 is considered abnormal and diagnostic of LPR [22]. However, RFS does not represent extra laryngeal findings with a low inter-rater reliability [7, 25]. **Table 3** illustrates the RFS score assessment.

5. Diagnosis

The diagnosis of LPR relies on a good history and clinical examination (including laryngoscopy), which is supported by investigation. Upper esophageal pH probe monitoring is the gold standard in monitoring patients with LPR [26], which is difficult to reproduce, time-consuming, requires specialized skills, incurs further investigative costs, and may not be readily available at healthcare institutions in rural areas.

The combination of RSI which explores the symptomatology and RFS which explores the physical findings are useful with its simple-to-fill questions to aid the diagnosis of LPR. RSI and RFS used simultaneously have been shown to have statistically significant differences in pre and posttreatment LPR. LPR may be chronic and/or intermittent. The combination of RFS and RSI in addition to history and clinical examination helps in the early diagnosis of LPR and immediate commencement of treatment, which minimizes the LPR-associated complications and eases treatment follow-up.

6. Management

The management of LPR is multidisciplinary and there are three components of management that should be considered. Refer to **Figure 9** for the illustrated treatment algorithm of LPR.

6.1 Lifestyle and dietary change

Since lifestyle factors, such as stress and behavior, contribute to an increase in gastric acid production, therefore it should be identified and managed effectively. Primary care physicians play a significant role in identifying these issues and managing them [27]. Psychological stress is believed to activate the mast cells *via* the autonomic nervous system, which releases mast cells, resulting in an increase in the permeability of epithelial cells. Acid and pepsin stimulate intraepithelial nociceptors, stimulating pain and the sensation of heartburn [28]. Diet and obesity are also significant contributing factors. Foods that may worsen acid reflux such as spicy diet (either chili or spices) and oily diet, which includes fried food, alcohol, caffeine (tea or coffee), carbonated drinks, and milk, are common causative factors [27–29]. In overweight or obese patients, weight loss is pertinent to reduce intra-abdominal

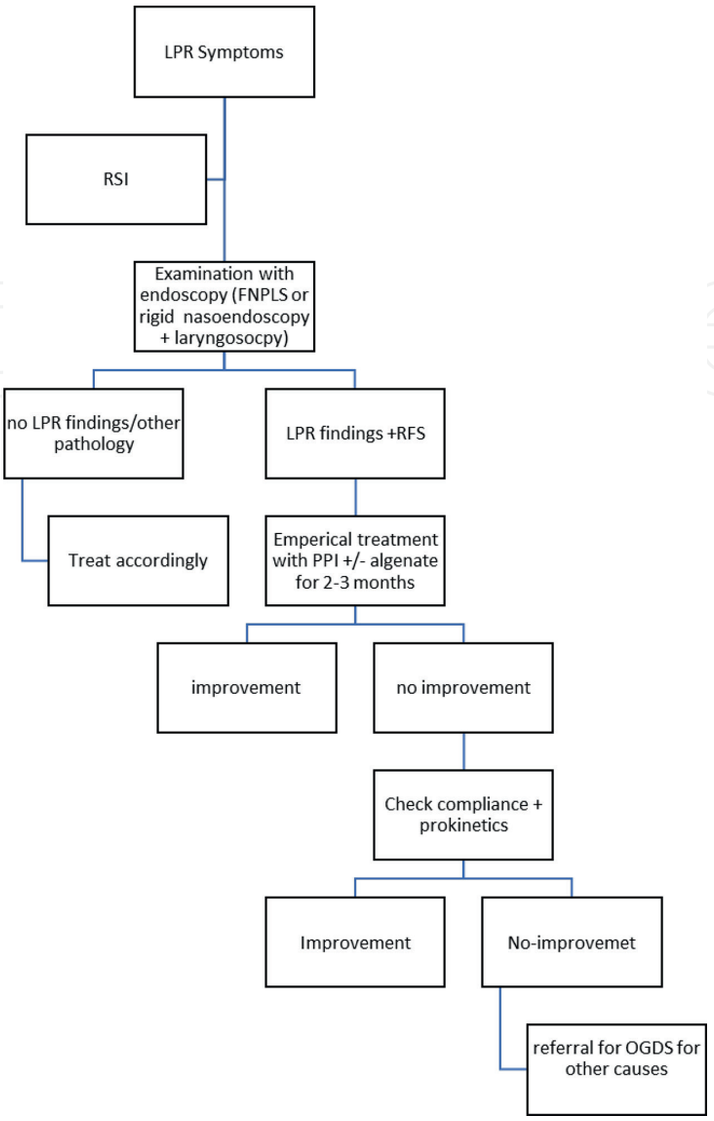

Figure 9.
Treatment algorithm for LPR.

pressure and improve esophageal sphincter function. Calorie restrictions and increasing activity levels can be managed by a dietitian and physiotherapist. Smoking, which is known to cause loosening of the lower gastroesophageal sphincter, should be stopped. A pharmacist may help with nicotine replacement therapy.

6.2 Pharmacotherapy

The mainstay of pharmacotherapy in managing acid reflux is the use of proton pump inhibitors (PPI). PPIs inhibit histamine-2–, gastrin-, and cholinergic pathways by irreversibly inhibiting the H + -K + ATPase proton pump on parietal cells, reducing the acidity and volume of gastric secretions. These, in turn reduce the availability of an acid medium for pepsin to function as an enzyme. PPIs should be consumed 30 to 60 minutes prior to meals, which allows for the highest concentration to inhibit gastric acid release during eating. Optimized administration of PPIs is twice daily doses of 40 mg of omeprazole or equivalent for 2 or 3 months [30]. These patients will need to be followed up with RSI and RFS scoring to assess improvements. It is believed that

GERD responds quicker to PPIs unlike LPR, which may improve in 3 months, but complete laryngeal symptomatic improvements may take up to 6 months [11].

There is a need to evaluate efficacy and diagnosis at 3 months and not hesitate to continue therapy and to ensure compliance with PPI therapy. Some may miss doses and not consume PPIs prior to meals. If there are improvements, this empirical therapy is indeed diagnostic and therapeutic to LPR [31]. If treatment is futile, there will be a need to revisit and revise the diagnosis. A referral to otorhinolaryngologist, gastroenterologist, or upper gastrointestinal surgeon for considerations of an OGDS and/or pH study shall there be no improvements at 2–3 months of optimum therapy. LPR symptoms are nonspecific, and these symptoms may hide another pathology within the esophagus and stomach. It is advisable to prevent prolonged dependency on PPIs, which are recently linked to chronic kidney disease. In Asian nations, H pylori is prevalent and should be ruled out as it contributes to acid reflux. The literature review has suggested a maximum therapy that involves addition of a H2 receptor antagonist at bedtime in addition to the two daily doses of PPIs before the morning and evening meals [11]. Prokinetic agents may be beneficial by speeding up gastric emptying and may be an option among patients with little benefit from optimum medical therapy. The literature is still unclear on its efficacy in LPR [32].

Pharmacotherapy for nonacid reflux involves alginates, which react with gastric acid to form a protective barrier to the upper intestinal mucosa, which is inexpensive and has an immediate onset of action by forming a barrier to protect the mucosa from further gastric acid irritation [11].

6.3 Surgery

Anti-reflux surgery is the step up and last resort of treatment if optimal pharmacotherapy has failed. For patients with significant hiatus hernia, laparoscopic fundoplication may be considered. A recent review of 844 patients found that laparoscopic fundoplication is beneficial with improvements in RSI among LPR patients resistant to pharmacotherapy [33]. Fundoplication has been effective in reducing heartburn, acid regurgitation, voice fatigue, chronic cough, choking, sore throat, and globus sensation. It was not very beneficial in alleviating throat clearing and adult-onset asthma [34].

7. Conclusion

LPR previously deemed a controversial topic in laryngology is now clearer with a better understanding of the pathogenesis. Diagnosis is made based on symptoms, and laryngoscopy aided with investigations and confirmed the response to treatment.

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