

*Review***Management of Laryngopharyngeal Reflux: A Practical Algorithm
Management for Primary care Physicians.**

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Abstract: Laryngopharyngeal reflux (LPR) is a prevalent disease in the general population and may have acute or chronic clinical presentation. LPR may be misdiagnosed in primary care medicine regarding the lack of gastroesophageal reflux disease symptoms and the lack of findings at the gastrointestinal endoscopy. Depending on the physician field of expertise and experience, LPR may be clinically over- or under-diagnosed. The management of LPR is possible in primary care medicine but primary care physician has to consider some red flags

that requires to address the patient to otolaryngologist or gastroenterologist. The use of patient-reported outcome questionnaire such as reflux symptom score-12 and the consideration of some oral and pharyngeal findings visualized through the mouth opening may help the primary care physician to evaluate the LPR findings at the diagnosis time and throughout treatment. In this review, we provide a practical algorithm of management of LPR for primary care physician or other specialists that cannot perform fiberoptic examination. In this algorithm, physician has to exclude some confounding conditions such as allergy or other causes of pharyngolaryngitis and red flags. Physician may prescribe an empirical treatment based on diet and behavioral changes with or without medication, depending on the complaint severity of the patient. In case of prescription of medication, proton pump inhibitors and alginate have to be considered in association to protect the upper aerodigestive tract mucosa from acid, weakly acid and alkaline pharyngeal reflux events.

Keywords: Reflux; Laryngopharyngeal; Gastroesophageal; Primary Care; Physician; Management; General; Treatment; Diagnosis.

DEFINITION

In 2002, the American Academy of Otolaryngology-Head and Neck Surgery defined Laryngopharyngeal Reflux (LPR) as the backflow of stomach contents into the laryngopharynx [1]. This definition of LPR has recently been considered incomplete because the irritation from LPR due to pepsin, bile salts and other gastroduodenal proteins does not involve only laryngopharyngeal mucosa but extends to all upper aerodigestive tract mucosa [2]. Indeed, LPR is often involved in the development of many laryngeal [3], rhinological [4], and otological [5,6] conditions. Currently, LPR is defined as an inflammatory condition of the upper aerodigestive tract tissues related to the direct and indirect effect of gastric or duodenal content reflux, inducing morphological changes in the upper aerodigestive tract [2]. The different definitions of LPR, which is also called ‘silent reflux’, ‘extra-esophageal reflux’ or ‘reflux laryngitis’, do not consider the evolution of complaints over therapeutic or non-therapeutic time. In practice, we may consider two types of LPR: acute and chronic LPR. Acute LPR may consist of the sporadic development of LPR-related symptoms and findings, which are both well-treated with an adequate treatment in patients who do not longer have chronic course of the symptoms. Chronic LPR may concern patients with chronic course of the LPR-symptoms with lack or poor therapeutic response or frequent recurrences of symptoms over time requiring

repeated therapeutic periods. In both definitions, LPR may be confirmed through objective testing or empirical treatment.

This paper aims to overview the current literature about LPR epidemiology, diagnosis and treatment. Based on the recent literature findings, we aim to provide practical findings and clinical algorithm for non-otolaryngologist and primary care physicians to manage LPR.

EPIDEMIOLOGY

Prevalence and Incidence

The establishment of both prevalence and incidence of a disease requires the use of a ‘gold standard approach’ to make the disease diagnostic. For LPR, the approach that may be considered as the ‘best gold standard’ is the hypopharyngeal-esophageal intraluminal impedance-pH monitoring (HEMII-pH). Nowadays, there is no study that evaluated the prevalence or incidence of LPR with HEMII-pH in general population or in outpatients consulting in otolaryngology department. However, some authors used alternative approaches that assessed the prevalence of LPR-symptoms or findings in the general or otolaryngological population. In 1991, Jamie Koufman estimated the LPR incidence at 10% of outpatients presenting to otolaryngology department with LPR symptoms and findings [7]. Koufman found that 30% of patients had documented acid pharyngeal reflux event according to dual-probe pH monitoring. In the same time, Gaynor evaluated that 1% of patients who visited primary care physician had symptoms suggestive of LPR, but no testing was performed to confirm the diagnosis [8]. The prevalence of LPR-related symptoms in the general population was evaluated in other studies through patient-reported outcome questionnaires and ranged from 5 to 30% of cases [9-11]. In fact, the exact prevalence and incidence of LPR are still unknown. According to the world region and the related diet and lifestyle habits, we may state, to the best of our knowledge, that LPR-symptoms could be found in 5 to 30% of individuals, making the role of the primary care physician important in the detection and the management of LPR.

Is LPR over- or under-diagnosed ?

The diagnosis of LPR is often presented as over- or under-diagnosed. In practice, because the symptoms and findings are both nonspecific [12], the detection of LPR is still complicated. According to some reports [13,14], LPR would be over-diagnosed, especially as cause of hoarseness. In a chart-review of 105 outpatients consulting in a voice clinic, Thomas *et al.* observed that dysphonia was often mis-attributed to LPR in patients with unapparent vocal fold

abnormalities [13]. Many otolaryngologists recognized that they may over-diagnose LPR regarding a survey conducted in 2014 [14]. However, many physicians do not commonly believe that LPR is over-diagnosed. In recent paper, Frazer-Kirk reminded that LPR is a common cause of upper aerodigestive tract disorders but may be under-diagnosed, especially regarding the lack of awareness about the clinical differences between gastroesophageal reflux disease (GERD) and LPR [15].

In practice, the risk to over- or under-diagnose LPR may depend on many factors, including the physician experience and knowledge about the LPR-symptoms and findings [16], the expertise area of physician [17], and naturally, the method used to perform the diagnosis. It is commonly recognized that the overvaluation of signs and symptoms related to LPR may be responsible for overdiagnosis of LPR [18], which strengthens the need to base the diagnosis on approach(es) that are as objective as possible.

PATHOPHYSIOLOGY

LPR is not GERD and GERD is not LPR

One of the most important point explaining the risk to under-diagnose LPR is the lack of awareness of physicians about the difference between LPR and GERD [19]. Many practitioners, including gastroenterologists and otolaryngologists, usually believe that *‘if the patient has no heartburn or GERD symptoms, there is no LPR’*. The studies demonstrated that LPR is not a simple extension of the esophageal refluxate into the upper aerodigestive tract. The Montreal criteria defined GERD as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications such as esophagitis [20]. The diagnosis may be investigated with pH study that, according to Johnson et DeMeester, has to report a length of time $>4.0\%$ of the 24-hour recording spent below pH 4.0 or a DeMeester score >14.72 [21]. In practice, patients with LPR may not have heartburn, esophagitis and they usually don't meet the GERD criteria of diagnosis at the pH study [22,23]. It is assumed that $\leq 50\%$ of LPR patients have GERD [24,25], while laryngopharyngeal complaints were present in 32.8% of GERD patients in the ProGERD study [25]. About pH study findings, LPR patients have more frequently gaseous, upright and daytime reflux events, and only 5.5% of pharyngeal reflux events occurred nighttime and recumbent [26]. Moreover, the gastrointestinal endoscopy may be normal in more than 44% of cases and may reveal esophagitis in 10 to 30% of LPR patients [26-28], whereas erosive esophagitis is found in almost 50% of GERD patients [29]. Barrett metaplasia is still rare in LPR patients [26-28]. Patients with Barrett's metaplasia had however

a higher rate of LPR than those with mild erosive esophagitis [30,31]. Others observed that patients with esophagitis have LPR findings in 24% of cases [32]. There is a correlation between the severity of GERD and the development of LPR [30]. About the LPR diagnosis, currently, there is no international consensual criteria to define LPR although some authors agree with the need to have more than 1 pharyngeal acid, weakly acid or alkaline reflux episodes at the HEMII-pH [2,22,23].

Pathogenesis and Pathophysiology

The clinical differences between LPR and GERD are related to distinct pathophysiological mechanisms. The occurrence of pharyngeal reflux event requires the opening of lower (LES) and upper esophageal sphincters (UES) that leads to the deposit of gastroduodenal content into the upper aerodigestive tract mucosa [2]. According to the type of epithelium, the reflux of pepsin, bile salts, trypsin and other gastrointestinal proteins into the upper aerodigestive tract mucosa leads to mucosal modifications including mucosal injury, inflammation reaction, mucus dryness, epithelium thickening and microtrauma. In vocal folds, pepsin may favor cell dehiscence, microtraumas and related benign lesions of the vocal folds [33,34]. The lesions would theoretically be less important in multistratified epithelium of the pharynx, which is more resistant than laryngeal mucosa. The high majority of studies focused on the impact of pepsin on laryngeal mucosa. Pepsin may be active with a pH ranging from 2 to 6, and induces intra- and extracellular damages that are associated with the development of an inflammatory reaction underlying both symptoms and findings [35,36]. Patients with LPR often complain of sticky mucus and xerostomia, which may be attributed to the dysregulation of type III anhydrase carbonic by pepsin. Anhydrase carbonic is an enzyme that ensures the hydration of mucosa through the following reaction: $H^+ + HCO_3^- \rightarrow 2 H_2O$ [37]. Accumulation of sticky mucus induces globus sensation, postnasal drip, throat clearing and cough.

Many grey areas

The pathophysiology of LPR is still incompletely understood. Four main research areas remain uninvestigated although they could provide substantial answers. First, the high majority of researches focused on pepsin but other enzymes could also play a key role in the development of mucosa the inflammatory reaction. Then, the role of trypsin, bile salts, elastase, gastric and pancreatic lipase enzymes in the mucosa injury remains uninvestigated. However, a few studies supported the refluxate of bile salts [38,39] without providing clear conclusion about the place of bile salts in the inflammatory process. Second, the stress and of the related autonomic nerve

dysfunction are probably involved in the development of LPR. The autonomic nerve dysregulation may lead to the increase of the opening of LES and UES, increasing the pharyngeal reflux events and the deposit of gastroduodenal content into the mucosa. Currently, only a few authors identified that LPR patients had autonomic nerve dysfunction, anxiety or stress [40,41]. Third, it is known that the laryngopharyngeal microbiota is important for the upper aerodigestive tract homeostasis. As for the lower digestive tube, bacteria have a critical role in the inflammation and the mucosa regeneration through the releasing of local anti-inflammatory molecules [42]. Currently, the role of LPR and the gastroduodenal refluxate on the microbiota remains unknown. This topic was however studied for GERD, metaplasia and esophageal microbiota [43], providing interesting findings such as the microbiota alteration by long-term proton pump inhibitor therapy [44]. Fourth, as practitioners, we know that, considering similar HEMII-pH features (number, duration and types of pharyngeal events), two patients will not develop similar clinical picture. The interindividual differences in the laryngopharyngeal mucosa sensitivity is probably one of the most important factors that underlies these clinical differences. To date, the laryngopharyngeal hypersensitivity condition was poorly studied in LPR disease.

CLINICAL PICTURE

Symptoms

The most prevalent symptoms associated with LPR are globus sensation, throat clearing, hoarseness, excess throat mucus or postnasal drip [2,12,45]. These symptoms, which are commonly observed in primary care medicine, are nonspecific and may be associated with active laryngopharyngeal allergy [2], rhinitis [46], chronic rhinosinusitis [47], smoking [48], alcohol abuse [49], and benign laryngopharyngeal infections [50]. In other words, it is difficult to base the LPR diagnosis only on laryngopharyngeal symptoms without objective examination or exclusion of these confounding factors. According to surveys, there may have mismatch between the prevalence of symptoms and the thoughts of otolaryngologists or gastroenterologists. Indeed, many specialists still believe that GERD-symptoms are prevalent in LPR and are essential to the diagnosis. Table 1 reports a comparison between the prevalence of symptoms found in clinical studies and the self-evaluated prevalence of LPR-symptoms by otolaryngologists [51,52]. To improve the diagnosis and the posttreatment evaluation of symptoms, Belafsky *et al.* developed in 2001 reflux symptom index (RSI) [53]. RSI is a 9-item patient reported outcome questionnaire assessing the severity of symptoms. A RSI>13 was

identified as suggestive of LPR. The mean weaknesses of RSI are the lack of consideration of some prevalent symptoms, such as throat pain, odynophagia, halitosis or regurgitations, and the lack of consideration of the symptom frequency [12]. For these reasons, reflux symptom score (RSS), which is a 22-item patient reported outcome questionnaires, was recently developed [54]. RSS considers the most prevalent otolaryngological, digestive and respiratory symptoms and evaluates symptom frequency, severity and the potential impact on quality of life. Patients fulfill RSS in 1 to 2 min, which may be considered as longer time for physicians. For this reason, based on the most prevalent and relevant findings identified in large cohort studies using RSS [23,26,54], a short version of RSS, the RSS-12, was developed [55]. RSS-12 consists of a 12-item clinical tool assessing both frequency and severity of the most prevalent LPR-related symptoms as well as their impact on quality of life (Table 2). RSS and RSS-12 reported better discriminative properties than RSI [54,55]. A RSS-12>11 is suggestive of LPR and is a practical clinical tool that may be used in general medicine to monitor the symptom evolution throughout therapeutic course. For patients with digestive complaints, the use of RSS, which include digestive items, makes sense.

Table 1: Real prevalence versus self-evaluated prevalence by otolaryngologists or gastroenterologists of LPR symptoms and findings.

Symptoms	Prevalence	OTOHNS	Findings	Prevalence	OTOHNS
<u>Digestive symptoms</u>			<u>Laryngeal</u>		
Heartburn	76.4	63.4	Arytenoid erythema	94.9	97.1
Stomach acid coming up	65.2	89.8	Posterior commissure hypertrophy	88.9	94.7
<u>Otolaryngological symptoms</u>			Interarytenoid granulations	41.5	88.2
Troublesome cough	59.6	95.5	Vocal fold erythema	11.3	85.7
Cough after lying down/meal	50.6	94.8	Endolaryngeal sticky mucus	78.5	80.7
Globus	73.0	92.5	Retrocricoid edema/erythema	70.3	85.9
Hoarseness	55.1	90.4	Vocal fold edema	2.0	77.9
Throat pain	68.5	85.2	Subglottic edema	4.0	59.8
Odynophagia	46.1	65.5	Subglottic erythema	11.1	63.6
Dysphagia	40.4	58.8	Vocal fold lesions	6.2	68.8
Chest pain	51.7	47.3	Laryngeal ventricle erythema/edema	46.5	71.5
Throat sticky mucus	69.7	88.7	<u>Pharyngeal & Oral</u>		
Throat clearing	76.4	93.9	Pharyngeal erythema	89.5	89.3
Tongue burning	29.2	72.5	Pharyngeal wall granulation	49.2	76.2
Halitosis	62.9	70.5	Anterior tonsillar pillar erythema	91.0	54.2
Breathing difficulties	42.7	42.3	Uvula erythema or edema	54.0	53.5
			Coated tongue	49.4	57.1
			Tongue tonsil hypertrophy	62.8	58.4

Table 1 footnotes: The prevalence of symptoms was assessed in a cohort study of 113 LPR patients [54]. The prevalence of the LPR-associated signs was determined in 101 patients with LPR disease regarding MII-pH [60]. The self-evaluation prevalence of both symptoms and findings were extracted from two surveys [51,52]. Abbreviations: OTOHNS=otolaryngologist-head and neck surgeons.

Table 2: Reflux Symptom Score-12

Reflux Symptom Score					
Within the last month, I suffered from one/several followed symptoms					
Severity: 0= problem is not severe, 5 = problem very troublesome when it occurs					
Frequency: 0= I don't have this complaint over the past month, 1;2;3;4 = I had 1-2;2-3;3-4;4-5 weekly over the past month; 5= complaint occurs daily					
	Disorder Frequency	Disorder Severity	Quality of Life impact		
			Total score		Total score
Ear Nose and Throat Disorders					
1. Hoarseness or a voice problem	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
2. Throat pain or pain during swallowing time	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Difficulty swallowing (pills, liquids or solid foods)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. Throat clearing (not cough)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
5. Sensation of something being stuck in the throat	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
6. Excess mucous in the throat and/or post nasal drip sensation	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
7. Bad breath	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
8. Heartburn, stomach acid coming up, regurgitations, burping or nausea	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
9. Abdominal pain or diarrhea	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
10. Indigesiton, abdominal distension and/or flatus	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
11. Coughing (not just throat clearing)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
12. Breathing difficulties, breathlessness or wheezing	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
RSS total score:.....			Quality of Life score:.....		

Table 2 footnotes: Severity item (5-point) is multiplied by frequency (5-point) to obtain symptom score (0-25). The sum is calculated to obtain RSS-12 final score (0-300). A RSS-12>11 is suggestive of LPR and exhibits high sensitivity (94.5%) and specificity (86.2%) [55].

Findings

The most prevalent findings associated with LPR include posterior commissure hypertrophy, arytenoid erythema, oropharyngeal and anterior pillar erythema (Table 1). As for symptoms, there may have discrepancies between prevalence and the thoughts of physicians. In 2001, Belafsky *et al.* developed reflux finding score (RFS) that rates the laryngeal findings associated with LPR [56]. RFS focuses on laryngeal findings and does not consider extra-laryngeal findings. The interrater reliability of RFS is low, limiting the reproducibility between otolaryngologists [57,58]. Regarding the weaknesses of RFS and the lack of clinical instrument considering both laryngeal and extra-laryngeal findings [59], reflux sign assessment (RSA) was developed (Appendix 1). RSA is a 16-item clinical instrument assessing LPR laryngeal and extra-laryngeal findings. The properties of RSA are better than RFS [60], but may be long to fulfill. Then, based on the initial version and its testing in clinical practice, a clinical short version of RSA is in process of validation. The development of RSA led to the identification of oropharyngeal and oral signs that are frequently associated with LPR. Anterior pillar erythema, coated tongue, uvula and oropharyngeal posterior wall erythema may be highly suggestive of LPR and are easily seen by the primary care physician (Figure 1) [61].

Figure 1: Oral and Oropharyngeal Findings Associated with LPR.

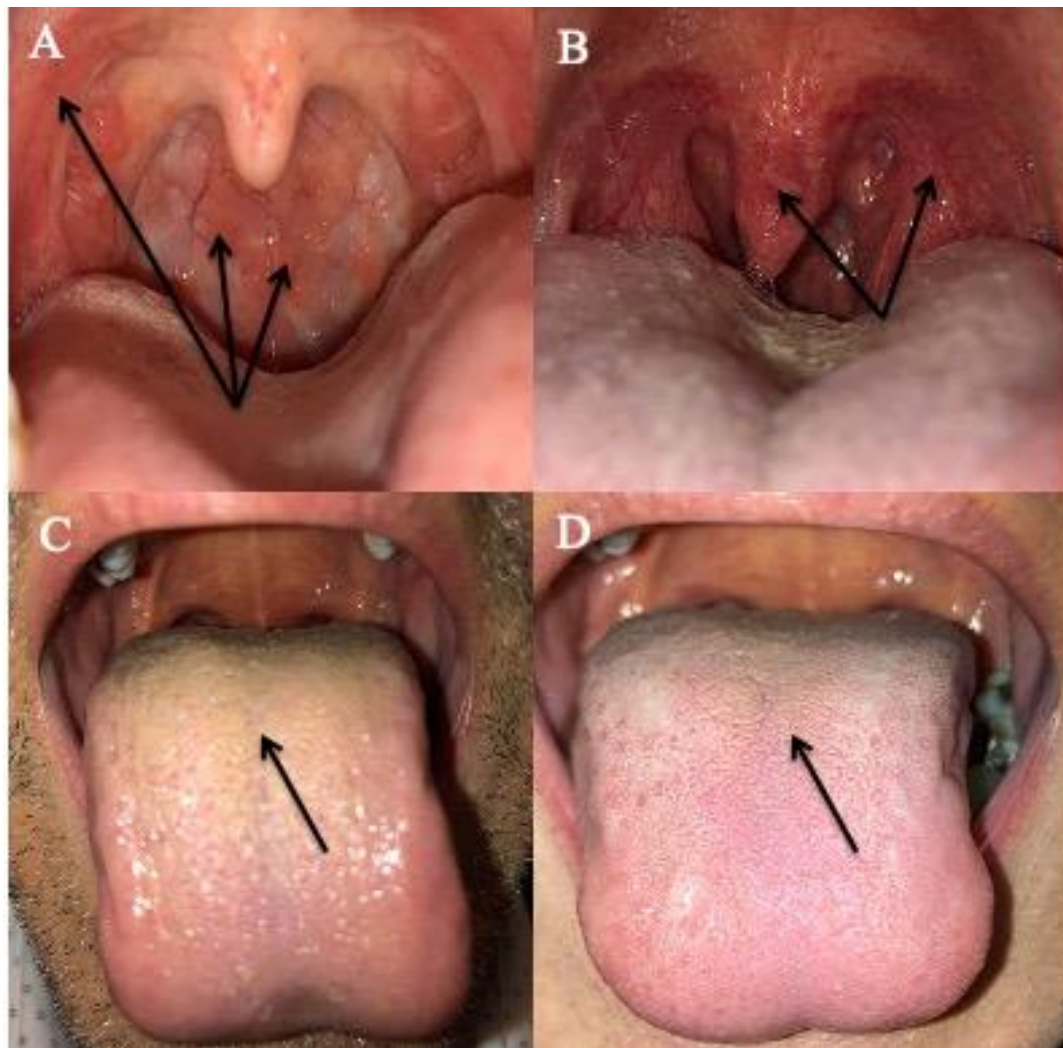


Figure 1 footnotes: Pharyngeal erythema (A), anterior pillar erythema (A, B) and uvula erythema (B) are signs easily identified in primary care practice (1, 2) accounting for 89.5, 91.0 and 54% of cases. Coated tongue (C) is found in 49.4% of patients and may significantly improved through treatment (D). However, primary care physician had to keep in mind that some patients have a significant improvement of symptoms but these signs may persist over time [71].

RSS-12 and the identification of these oral and oropharyngeal findings may be both used in primary care medicine for the diagnosis and the evaluation of therapeutic response. The primary care physician has to be aware about the LPR signs and symptoms in children or adult with chronic dental disorders, i.e. decays or erosion, with regards to the potential association between LPR and these common conditions [62,63].

The lack of knowledge about the association between LPR and some extra-laryngeal signs and symptoms of LPR often led to misinterpretation of the clinical picture of the patient. Thus, we often met LPR patients who taken several lines of antifungal drugs for coated tongue, misattributed to mycosis, while others received antibiotics or underwent tonsillectomy for recurrent LPR-associated throat pain. The role of primary care physician remains important to avoid inadequate management of these conditions. Naturally, as for symptoms, the LPR signs are nonspecific and may be encountered in many common conditions including smoking, alcoholic pharyngolaryngitis, chronic rhinosinusitis or acute/recurrent infectious diseases. The primary care physician has to evaluate all confounding factors and, in case of doubt, address the patient to otolaryngologist who could perform nasofibroscopy.

Red flags for the primary care physician

When to Address patient to Otolaryngologist ?

In many healthcare systems, the primary care physician is the first line physician. In that way, its role to detect, treat and, in case of difficulties, address the patient to specialist is crucial. The primary care physician may address the patient to specialist when he is confronted to difficulties or '*red flags*'. The appearance of LPR symptoms or findings in patients consuming tobacco or alcohol requires the realization of an ear, nose, and throat (ENT) fiberoptic examination to exclude malignancy. Some symptoms have to be particularly considered, including dysphonia, dyspnea, hemoptysis, neck nodes or weight loss. Note that ear pain or throat pain may be usually associated with LPR and do not require ENT examination. The anamnesis has to dissociate LPR-related ear or throat pain than ear or throat pain in a suspected context of malignancy. Moreover, all physicians have to keep in mind that patients who respect the antireflux diet often loss weight.

About patients with history of chemo/radiation, it is important to keep in mind that radiation may impact the salivary gland function and the hydration of upper aerodigestive tract mucosa, which are usually associated with laryngopharyngeal symptoms. However, the development of new or unusual symptoms in patients with history of head and neck cancers or radiation may be considered as another red flag. Some reports supported that the mucosa inflammation related to reflux may lead to dysphagia and aspirations [64,65], especially in elderly patients who suffered from presbyphagia. These patients may benefit from an ear, nose and throat consultation to identify the occurrence of aspirations and to prevent the related risk of pneumonia.

When to Address patient in Gastroenterologist ?

The majority of gastroenterologists commonly manage LPR patients who often have both gastrointestinal (GI) and laryngopharyngeal symptoms. Some conditions have to be considered as red flags and may require a GI examination. According to the relationship between LPR, severe GERD, esophagitis and Barrett metaplasia [30,31], LPR patients with heartburn or non cardiac chest pain has to benefit from GI endoscopy. The identification of this red flag is however more complicated in elderly patients who may have esophagitis or Barrett metaplasia without symptoms regarding the deterioration of esophageal nerve endings [66,67]. In that way, chronic symptoms in patients >50 years old have to be evaluated by specialist. The occurrence of recurrent regurgitations, hypersalivation, weight loss or GI bleeding are other red flag supporting the realization of GI endoscopy to exclude esophageal lesion, dysmotility, Zenker diverticulum or other dysmotility diseases. Patients without response to an empirical treatment based on PPI and alginate and those with a family history of upper GI cancer also have to be evaluated in gastroenterology [68,69]. The main red flags that have to address patient in otolaryngology or gastroenterology are summarized in Table 3.

Table 3: Red flags requiring Specialist Consultation.

Red flags that support to refer patient to	
Otolaryngologist	Gastroenterologist
1. Onset of symptoms in alcoholics/smokers.	1. Symptoms including severe heartburn and chest pain.
2. Onset of modification of symptoms in patients with a history of head neck malignancy.	2. Symptoms including severe dysphagia, hypersalivation, or vomiting.
3. Symptoms and neck nodes lasting for >3 weeks.	3. History of untreated Barrett metaplasia.
4. Weight loss without diet and lifestyle habit changes.	4. Chronic symptoms in patient >50 years old.
5. Aspirations and lung infections.	5. Unvoluntary weight loss >5% of weight.
6. Voice professionals with severe dysphonia or patients with dysphonia lasting for >3 weeks.	6. Unexplained associated Iron deficiency.
7. Hemoptysis or dyspnea.	7. Gastrointestinal bleeding.
	8. Associated neck lymphadenopathy.
	9. Family history of upper digestive cancer.
	10. Non-response to empirical treatment.

Table 3 footnotes: -.

ADDITIONAL EXAMINATIONS

Hospital examinations

Hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring and Oropharyngeal pH study

HEMII-pH detects esophageal bolus movement by measurement of changes of electrical resistance and may measure the pH of the refluxate through 3 pH sensors located in the low, upper esophagus and in the pharyngeal cavity. HEMII-pH is usually well tolerated and may represent a cost-effective approach [70]. The indications of HEMII-pH are not standardized. Nowadays, HEMII-pH is used in nonresponder patients to an empirical therapeutic trial or those with many confounding factors (allergy, chronic rhinosinusitis, etc.) yielding the diagnosis unclear. The use of HEMII-pH in patients with moderate-to-severe LPR symptoms is increasingly considered as a cost-effective approach because that allows the prescription of personalized treatment considering the LPR features (acid, weakly acid or alkaline; upright/daytime *versus* supine/nighttime) [70]. Such treatment is associated with good outcomes, the possibility to reduce drug doses through the treatment, and the weaning at 3 to 9 months [71]. Because the most accepted criteria of LPR diagnosis is the occurrence of more than 1 pharyngeal reflux episode, Restech® developed a novel pH study device using an unique pH sensor into the pharynx (Restech®, Respiratory Technology Corp. San Diego, USA). This device is easy to use but, as for HEMII-pH, the analysis and the diagnosis criteria have to be standardized [2].

Gastrointestinal endoscopy

As above-mentioned, GI endoscopy has a limited role in the management of LPR. Primary care physicians may prescribe GI endoscopy in patients with heartburn, chest pain or GI symptoms but has to keep in mind that a normal GI endoscopy does not exclude the LPR diagnosis. As suggested in table 3, elderly patients may have esophagitis without complaints; then, GI endoscopy may be useful for >50 years old patients with chronic symptoms.

In-office examination

The detection of pepsin on saliva is possible in the primary care physician office through the peptest® device (Peptest™ kit; RD Biomed Ltd., Hull, United Kingdom). Patient has to collect 2 or 3 saliva samples and the physician performs the measurement of pepsin saliva concentration respecting a standardized procedure lasting 15 to 20 minutes. The physician used the Cube Reader® that detects pepsin down to 16 ng/mL. As recommended [72], the test was considered as positive when the pepsin level reached 36 ng/mL. Considering MII-pH as the gold standard, meta-analyses suggested that both sensitivity and specificity of peptest would be 64% and 68%, respectively [73,74]. There would have many grey area limiting the establishment of clear indications for peptest. First, the saliva pepsin concentration would be not correlated with the HEMII-pH findings, especially the number and the duration of pharyngeal reflux events [75]. Second, the diet of patients

could have a significant impact on the pepsin saliva concentration [76]. Third, there is no consensus about the best time of saliva collection [74]. Some authors supported that the peptest of the morning would be the most reliable [76,77] but that has to be confirmed in future studies. Peptest is a promising method in the detection of LPR and could be used in primary care medicine at the office of the primary care physician.

TREATMENT

Cost-effective Empirical Approach

Over the past few decades, the empirical therapeutic trial based on proton pump inhibitors (PPIs) was proposed as the main cost-effective approach to treat and support the LPR diagnosis [78-81]. Nowadays, this approach is increasingly tempered for many reasons [70,82]. First, PPIs are suspected to have short- and long-term side effects (Table 4) that support the PPI prescription only in patients with an identified acid reflux disease and for the shorter duration [70].

Table 4: Long-term Side Effects of Proton pump inhibitors.

Systems	Presumed side effects of PPI	Status
Stomach	Increased risk of gastric neoplasia	Highly suspected
	Increased risk of Vitamin B12 deficiency	Suspected
	Increased risk of Calcium deficiency	Suspected
	Increased risk of Iron deficiency	Suspected
	Increased risk of Magnesium deficiency	Suspected
Digestive	Increased risk of bacterial, parasitic, and fungal infections	Suspected
Liver	Increased risk of Cancer	Suspected
	Increased risk of Bacterial overgrowth	Suspected
Kidney	Increased risk of Acute Interstitial Nephritis	Highly suspected
	Increased risk of Chronic kidney disease	Suspected
Bone	Increased risk of Osteoporosis & fracture	Suspected
Brain	Increased risk of Dementia	Highly suspected
Chest	Increased risk of pneumonia*	Suspected
Cardiovascular	Increased risk of cardiovascular events**	Suspected
	Increased risk of electrolyte imbalances	Suspected

Table 4 footnotes: The association between proton pump inhibitors and many disorders is suspected or highly suspected [70]. *The association between PPI use and pneumonia risk was particularly found in elderly patients, patients admitted in intensive care unit, with dementia, with a history of acute stroke, type 2 diabetes, or cirrhosis, and those with chronic GERD. ** There will be an interaction between clopidogrel and PPIs; underlying the increased risk of cardiovascular events in patients who take clopidogrel and PPIs. Abbreviations: GERD=gastroesophageal reflux disease; PPI = proton pump inhibitor. Abbreviations: PPIs=proton pump inhibitors.

Second, the response to PPI does not tell the treating physician what to do with non-responders, while it is possible that those with persistent cough, globus sensation, throat clearing, and/or other presumed LPR symptoms may actually not have LPR if they do not respond to empiric treatment. It is possible that refractory or alkaline LPR may be present; this would be identified by HEMII-pH, but cannot be excluded on the basis of empiric treatment [2,70]. Alkaline and weakly acid LPR are more prevalent than previously presumed because they concern more than 50% of patients [83,84] and, therefore, require alginate therapy to control the alkaline component of reflux. Note that alginates are also interesting for GERD and acid LPR. Third, the PPI effects on LPR disease are still controversial since meta-analysis of placebo-RCTs did not find superiority of PPIs over placebo [12,85]. All of the arguments explain why the use of empirical PPI treatment is still controversial. In practice, an empirical treatment has to include diet, PPIs and alginate medication to ensure an efficacy on all types of LPR [70]. An adequate antireflux treatment may be helpful for the reflux symptoms but also for other conditions of the patients, such as sleep disorder [86], overweight [2] or dental disorders [62]. The primary care physician usually knows the lifestyle and the behavior of these patients. In that way, he could have a critical role to strengthen the relevance of diet in both the suspected or confirmed LPR disease. Because the LPR is often due to diet habits [87,88] and stress [89], the primary care physician has a key role to sensitize the patient about these favoring factors and to prevent recurrence or chronic course of the disease. Some scores assessing the refluxogenic potential of diet were developed [90,91] and, through mobile phone App, could be useful for patients in the choice of their favorite foods. Some foods and beverages are associated with a high risk of reflux while others are protective regarding LPR (Tables 5 and 6). The awareness of patients about the importance of diet is crucial in the short to long-term management of LPR and the role of the primary care physician is crucial. Similar findings have to be considered for the management of stress and anxiety, which both lead to autonomic nerve dysfunction and transient esophageal sphincter relaxation [40,41,89]. A practical algorithm of management of LPR by primary care physician is proposed in Figure 2. In summarize, to be cost-effective, primary care physician may propose an empirical treatment based on diet and stress management for patients with mild LPR and no red flags, while for the others, the empirical treatment has to include PPIs and alginate for 2 to 3 months.

Table 3: The Refluxogenic Diet Score of foods and their Refluxogenic Potential.

Asparagus*	0,072	1	Banana	0,227	2	Blueberry	0,472	3	Blackberries	0,640	4	Bacon	25,40	5
Baked spinach	0,025	1	Carrots	0,132	2	Boiled egg	0,348	3	Brie, Blue, bread cheeses	1,001	4	Butter	-	5
Beetroot	0,082	1	Cherry	0,243	2	Camembert	0,495	3	Cake	1,850	4	Candy or sweets	5,216	5
Broccoli	0,077	1	Chicken fillet	0,148	2	Cereals (corn flacks)	0,470	3	Cauliflower	0,596	4	Chocolate (dark)	4,171	5
Brussels sprout	0,030	1	Chilli	0,171	2	Courgettes	0,289	3	Cheddar	1,068	4	Chocolate (Milk)	3,787	5
Celery	0,101	1	Corn	0,244	2	Cucumber	0,274	3	Chocolate cookies	1,920	4	Chocolate (white)	4,543	5
Cooked mushrooms	0,103	1	Fat chicken	0,236	2	Dried plum	0,252	3	Cookies	1,695	4	Chocolate croissant	2,911	5
Crabs	0,088	1	Fennel	0,131	2	Duck (without skin & fat)	0,350	3	Cracker	0,952	4	Chocolate eclairs	2,079	5
Egg white	0,006	1	Ketchup**	0,166	2	Fat fish	0,368	3	Egg yolk	1,334	4	Croissant	2,860	5
Endive	0,014	1	Kidneys	0,192	2	Fig	0,267	3	Feta	1,501	4	Curry	2,985	5
Fresh & thin fish	0,058	1	Lamb	0,232	2	Fish oil (sardines, cods)	-	3	Fontina	0,946	4	French fries & frying	2,836	5
Garlic	0,035	1	Lamb chops or shoulder	0,201	2	Fish oil (herrings)	-	3	Goat cheese	1,061	4	Ice cream	3,364	5
Green beans	0,054	1	Leek	0,139	2	Fish sauce	0,428	3	Gouda	1,193	4	Macadamia nut	7,074	5
Green peas	0,095	1	Melon	0,189	2	Ginger	0,362	3	Ground meat	0,704	4	Mayonnaise	56,80	5
Green salad*	0,074	1	Oat	0,243	2	Grapefruit	0,392	3	Gruyere	0,992	4	Meat sauce (Bearnaise)	45,04	5
Honey	0,000	1	Onion*	0,129	2	Guava	0,376	3	Hard cheese, full-fat cheese	1,093	4	Meat sauce (Pepper)	3,839	5
Horse	0,076	1	Parsley	0,139	2	Lamb cutlets	0,462	3	Kiwi	0,540	4	Meat sauce (Roquefort)	3,060	5
Lentil	0,064	1	Pepper	0,186	2	Mandarin	0,478	3	Lychee	0,512	4	Milk (coco)	6,521	5
Low-fat cheese	0,003	1	Pork tenderloin	0,208	2	Milk (goat, semi-skimmed)	0,272	3	Mango	0,536	4	Nut, cashew, hazelnut	3,585	5
Milk (Skimmed)	0,030	1	Rib steak	0,153	2	Milk (soja)	0,298	3	Meat sauce (Mushroom)	1,116	4	Olive (black)	7,478	5
Mollusk	0,060	1	Ribs	0,246	2	Milk (Semi-skimmed)	0,363	3	Milk (whole)	0,690	4	Oliver (green)	12,92	5
Pork roast	0,110	1	Rice (Brown)	0,188	2	Mint	0,302	3	Mozzarella	1,025	4	Pasta sauce (carbonara)	2,071	5
Pumpkin	0,085	1	Rindless, fatless,	0,131	2	Nectarine	0,292	3	Munster	1,223	4	Pasta sauce (pesto)	8,331	5
Red cabbage	0,046	1	Cooked ham	0,131	2	Olive oil	-	3	Mustard	1,839	4	Pesto	8,331	5
Rice (Red)	0,121	1	Rye bread	0,166	2	Orange	0,381	3	Noodles	0,565	4	Potato chips	2,830	5
Rice (White)	0,089	1	Shallot*	0,201	2	Peach	0,361	3	Orange jam	0,623	4	Sauerkraut	5,696	5
Roast veal	0,090	1	Steak, fillet, striploin	0,208	2	Pear	0,364	3	Parmesan	0,836	4	Spicy##	0,000	5
Shrimps or lobster	0,033	1	Tofu	0,248	2	Pickle	0,270	3	Pasta sauce (bolognese)	1,134	4			
Spaghettis (cooked)	0,060	1	Turnip	0,186	2	Plum	0,471	3	Pâté	1,612	4			
Sweet potato	0,073	1	Veal chop	0,181	2	Pork chops and shoulder	0,316	3	Peanut	1,618	4			
Tuna (low-fat)	0,043	1	Watermelon	0,175	2	Potato	0,357	3	Pomegranate	0,725	4			
Turkey fillet	0,026	1	White bread	0,187	1	Raspberry	0,307	3	Raisin	0,758	4			
Veal cutlet	0,059	1	Whole ham	0,236	2	Rhubarb	0,362	3	Raspberry jam	0,566	4			
Wheat	0,079	1				Salmon	0,375	3	Redcurrant	0,922	4			
						Sardines	0,290	3	Ricotta	1,030	4			
						Strawberry	0,340	3	Roquefort	1,288	4			
						Sugar#	0,000	3	Salami	1,177	4			
						Tomato (raw)	0,297	3	Sausages	0,722	4			
						Tripes	0,255	3	Sorbet	1,942	4			
						Wholemeal/brown bread	0,264	3	Strawberry jam	0,618	4			
									Tomato sauce	1,538	4			
									Vinaigrette	-	4			
									Yoghurt (fat)	0,674	4			

Table 5 footnotes: Categories 1 and 2 correspond to low refluxogenic foods while categories 4 or 5 include foods with a high or very high refluxogenic potential [90,91]. Some foods may be upgraded or downgraded regarding to characteristics. *Raw vegetables are less digestible and may be associated with low gastric emptying time: in case of raw consumption, the food has to be upgraded for 1 category. Not for green salad, the addition of vinegar or vinaigrette upgrades the category. **In case of addition of spicy (for example, Spicy Ketchup), these foods have to be upgraded. #For sugar, only the pH and the glycemic index have been considered regarding the lack of fat. ##Because spicy has no lipid and no pH, the authors based the classification of this food on the literature. If the patients only eat industrial foods (ready-made food), the foods may be upgraded regarding the acidifying potential of industrial conservative. Abbreviations: REDS=refluxogenic diet score.

Table 6: The Refluxogenic Diet Score of beverages and their related categories.

Juice, water and alcohol	pH	GI>40	Cat.	UCat.
Alcohol (strong & licor)*°	4	+	3	5
Aloe vera	6,1	0	2	2
Apple juice	3,65	+	4	5
Beer # (°)	4	+	3	5
Cacao (hot chocolate)	6,3	+	2	3
Chamomile	6,5	0	2	2
Chicory	5,95	0	3	3
Coffee**	5	0	3	4
Grapefruit juice	3,05	+	4	5
Lemon juice	2,3	+	4	5
Multifruit juice	3,8	+	4	5
Orange juice	3,5	+	4	5
Soda (sugar free) #	2,5	0	4	5
Soda (with sugar) #	2,5	+	4	5
Syrup (Mint,lemon,grenadine)	2,15	+	4	5
Tea**	5	0	3	4
Tea (blackberry)**	2,5	0	4	5
Tea (black)**	5,3	0	3	4
Tea (green)**	7	0	2	3
Tea (lemon)**	2,9	0	4	5
Tomato juice	4,35	0	3	3
Water (sparkling) #	7	0	2	3
Water (still)	7	0	2	2

Water (alkaline)	8	0	1	1
Wine (red) [°]	4	0	4	5
Wine (rose) [°]	4	0	4	5
Wine (white) [°]	4	0	4	5

Table 4 footnotes: The classification of beverages depends on pH, *glycemic index (GI; high sugar-related osmolarity), #sparkling (upgrade), °the alcohol degree (>3%=upgrade) and the **presence or lack of caffeine or theine (**upgrade or downgrade). Abbreviations: GI=glycemic index; cat.=category at baseline; ucat.=upgraded category. For hot chocolate, the category is upgraded in case of additional sugar.

Figure 2: Practical algorithm of Management of Laryngopharyngeal Reflux in Primary care Medicine.

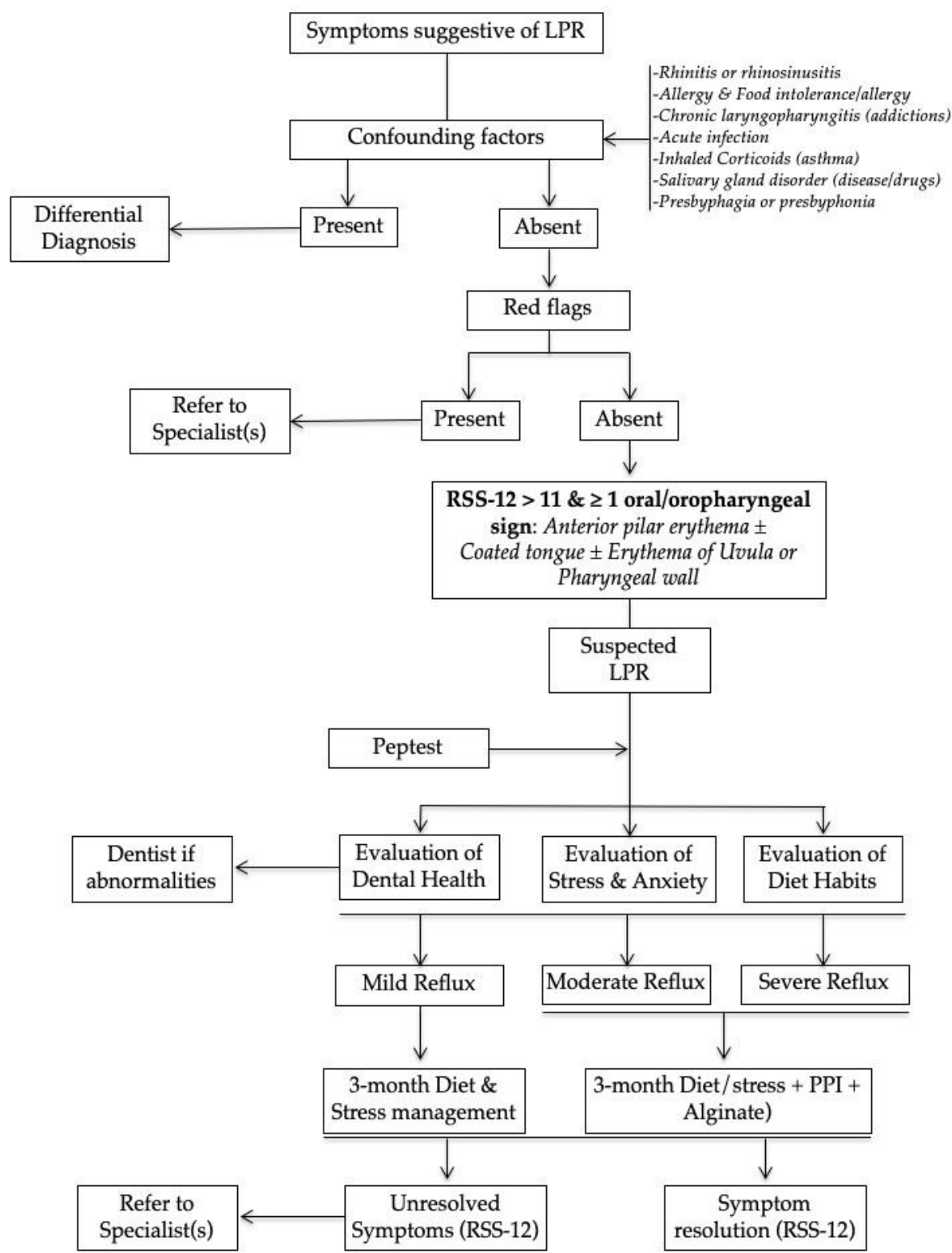


Figure 2 footnotes: Abbreviations: LPR=laryngopharyngeal reflux; PPI=proton pump inhibitors; RSS-12=reflux symptom score-12.

CONCLUSION

To date, it seems possible that a high number of primary care or general physicians are still unaware of the entity laryngopharyngeal reflux [92]. However, many LPR may be managed by primary care physicians if they consider the use of clinical tools describing symptoms and signs associated with LPR, the exclusion of some confounding conditions, the relevance of some red flags and the use of an appropriate therapeutic approach. In this study, we propose a practical algorithm to manage LPR in primary care medicine. The reliability of this algorithm has to be evaluated in future studies as well as the use of peptest as diagnostic method in the primary care practitioner office.

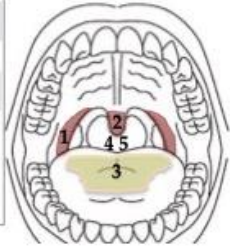
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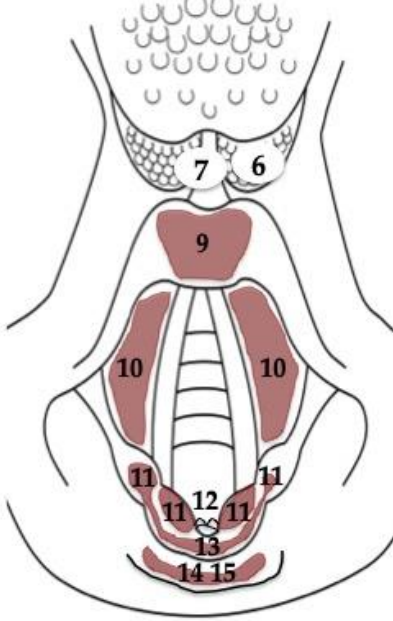
Author Contributions: Conceptualization, JRL, PDK. and SS; Methodology/Organization, MRB, VM, CC; Writing – Original Draft Preparation, JRL, VM, SS; Writing – Review & Editing, PKD, SS, SH; Supervision, SS, SH, PDK.

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Appendix A; Reflux Sign Assessment.

1 Erythema of anterior pillar 0 = absent 4 = present 2 Uvula edema ± erythema 0 = absent 3 = present 3 Coated tongue 0 = absent 2 = present Oral Cavity RSA: .../9		4 Oro- hypopharyngeal erythema 0 = absent 4 = present 5 Oro- hypopharyngeal granulation 0 = absent 3 = present 6 Tongue tonsil hypertrophy 0 = absent 3 = mild/moderate 4 = severe <small>Apparent vallecula Apparent vallecula when tongue stuck Unapparent vallecula</small>	Pharyngeal RSA: .../19 7 Pharyngeal sticky mucus 0 = absent 4 = present 8 Contact between epiglottis & base of tongue 0 = absent 4 = present
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9 Erythema/edema of the epiglottis 0 = absent 3 = present 10 Erythema/edema of the ventricular band 0 = absent 2 = present 11 Laryngeal erythema 0 = absent 4 = located to arytenoids 5 = diffuse 12 Inter-arytenoid inflammatory granulations 0 = absent 2 = present 13 Posterior commissure hypertrophy 0 = absent 5 = present 14 Retrocricoid erythema 0 = absent 3 = present 15 Retrocricoid edema 0 = no contact with hypopharyngeal wall (open glottis) 4 = contact with hypopharyngeal wall (open glottis) 16 Endolaryngeal sticky mucus 0 = absent 3 = present 17 Vocal fold granuloma 0 = absent 2 = present Laryngeal keratosis 0 = absent 2 = present Vocal fold ulceration 0 = absent 2 = present Laryngeal RSA: .../33		RSA total score: .../61
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The tool is subdivided into three parts according to the sign localization: oral cavity, pharynx and larynx. The occurrence of vocal fold granuloma (+2), keratosis (+2) or ulceration (+2) may be considered in the last item of the score. Because low prevalence, the following items were removed from the initial version of RSA (in the RSA validation paper): edema/erythema of the vocal folds, nasopharyngeal erythema, and subglottic edema/erythema. The total score is calculated by the sum of each item score. The maximum score is 61.

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