Laryngopharyngeal reflux disease: clinical presentation, diagnosis and therapeutic challenges in 2018

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REVIEW

Laryngopharyngeal reflux disease: clinical presentation, diagnosis and therapeutic challenges in 2018

Jerome R. Lechien[a,b,c,d], *Sven Saussez*[a,b,d], *and Petros D. Karkos*[a,e]

Purpose of review
To review the recent literature on presentation, diagnosis and treatment of laryngopharyngeal reflux.

Recent findings
Patients with laryngopharyngeal reflux have a higher risk for gastroesophageal reflux and respiratory-related diseases. Many symptoms and findings are underestimated, contributing to the inconclusive results of many therapeutic trials. Additionally, little significance is given to nonacid and mixed refluxates, although a significant prevalence. The association between symptoms, signs, impedance-pH studies and pepsin detection could be the most accurate way for a clear diagnosis. 'Reflux profiling' is also important for the administration of a personalized treatment based on diet, proton pump inhibitors, alginate, magaldrate and other second-line drugs. There are only a handful of studies focusing on the addition of alginate or magaldrate to the treatment of laryngopharyngeal reflux, although their contribution has extensively been demonstrated.

Summary
Diagnosis remains controversial despite improvement in impedance and availability of pepsin detection in daily practice. With recent studies exhibiting a significant prevalence of nonacid or mixed refluxes, the addition of alginate or magaldrate to proton pump inhibitors should be considered. Future studies are needed to assess these new therapeutic schemes in moderate and severe laryngopharyngeal reflux.

Keywords
diagnosis, laryngitis, laryngopharyngeal, reflux, treatment

INTRODUCTION

Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissues related to direct and indirect effect of gastroduodenal content reflux, which induces morphological changes in the upper aerodigestive tract [1▪▪]. This definition differs from the past definition of the 2002 position statement of American Academy of Otolaryngology-Head and Neck Surgery [2] that did not take into consideration the irritation of some duodenal molecules [3,4] into all upper aerodigestive tract mucosa (and not only into the laryngopharynx), and the possible multifactorial origin of some symptoms that can be triggered by neuroreflexive signaling and compensatory vagal responses (indirect effect) [5]. Over the last three decades, the number of LPR publications has progressively increased (Fig. 1), however, despite this enthusiasm, it still remains a controversial topic particularly when dealing with clinical assessment, diagnosis and treatment. The purpose of this article is to review the recent literature on clinical presentation, diagnosis and treatment and to propose a complete management algorithm of LPR.

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KEY POINTS

- LPR is a prevalent disease in otolaryngology but the exact incidence and prevalence remain unknown.
- A large number of patients may concomitantly have LPR, GERD, and respiratory-related disorders that need the use of multidimensional clinical tools for the diagnosis and the therapeutic outcomes.
- Many symptoms and findings are not described in the current patient-reported outcome measures and instruments evaluating the clinical findings of laryngopharyngeal reflux.
- Future diagnosis may associate symptoms, upper aerodigestive tract findings, impedance-pH metry, pepsin and trypsin detections. This approach will help to determine a patient profile with laryngopharyngeal reflux for personalized treatment.
- Diet can be sufficient treatment for mild LPR whereas alginate or magaldrate are required for mixed and nonacid reflux, respectively. Long-term control of reflux requires diet and lifestyle modifications.
- Therapeutic efficiency evaluation must include changes of signs and symptoms. Compliance with medication intake is often the cause for resistant patients. When resistance is confirmed with good compliance to diet and medication recommendations, additional examinations are required to propose second-line treatment.

EPIDEMIOLOGY

There is a consensus that recognizes LPR as one of the most frequently encountered chronic inflammatory conditions of upper aerodigestive tract, but real incidence and prevalence are inaccurate and difficult to estimate worldwide because of lack of diagnostic criteria. Since the initial work by Koufman [6] that estimated the LPR incidence at 10% of the ear, nose, and throat (ENT) outpatients, only a few epidemiological studies have been published. In China and Greece, the LPR prevalence was estimated to 5 and 18.8%, respectively, but these evaluations were only based on patient-reported outcomes questionnaires that are insufficient to make the diagnosis [7,8]. In another report from a tertiary voice center, an evaluation of the prevalence of patients with LPR complaints was carried out during a 5-month period. With pH monitoring, the author showed that 69% of patients had LPR symptoms and findings and 50% of total patients had positive pH monitoring (defined as pH <4 in the esophageal probe, $\geq$8.1% upright and 2.9% supine) [9]. Since this initial report, there is no additional study evaluating incidence or prevalence of LPR in voice center with objective examination. To get precise LPR incidence and prevalence rates, future conducted studies will need to include 24-h multichannel intraluminal impedance-pH metry (MII-pH metry) or a future best diagnostic tool in all patients with

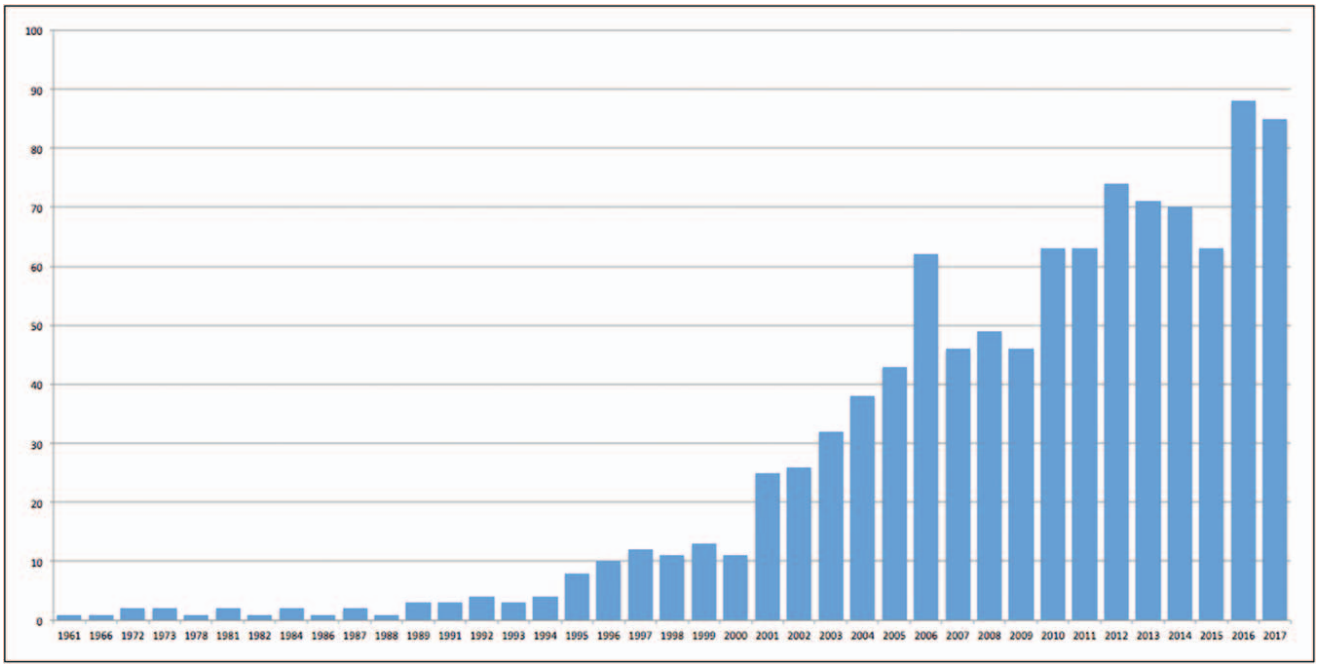

FIGURE 1. The evolution of publications about laryngopharyngeal reflux during the past six decades. To identify publications about LPR, we performed a systematic electronic research on PubMED with the following keywords. 'laryngopharyngeal,' 'laryngitis,' 'reflux,' 'gastroeosophageal.' This graph shows the total number of publications performed about laryngopharyngeal reflux according to the year. LPR, laryngopharyngeal reflux.

LPR signs and symptoms presenting at the ENT consultation. The incidence and prevalence of LPR is particularly important when considering the increase in junk food [10–12], obesity, acidification of foods [10], and the increase in risk factors for gastroesophageal reflux disease (GERD) and LPR in western countries [8,13–15].

Clinical presentation

Sign and symptom pathogenesis

LPR disease develops following macroscopic [16,17] and microscopic [17,18▪▪] changes of the upper aerodigestive tract mucosa. Mucosal irritation leads to an inflammatory reaction and dry (sticky) mucus hypersecretion, as pepsin decreases the expression of mucin and the secretion of bicarbonate [3,17,19]. The accumulation of sticky mucus triggers symptoms such as postnasal drip sensation, globus sensation, and throat clearing, leading to cough and choking [20]. Mucus hypersecretion and related complaints can also be mediated by stimulation of mucosal chemoreceptors in the distal portion of esophagus, irritated by refluxed material from the stomach [5,21]. At the same time, mucosal inflammation of the upper aerodigestive tract may induce dysphagia, globus sensation, throat pain, and odynophagia. The pathophysiological mechanisms underlying the development of hoarseness are more complicated and, according to a recent pathophysiological model, involves macroscopic and microscopic histological changes in the mucosa of the vocal folds [17] and substantial modifications of biomechanical properties of the vocal folds leading to subjective and objective voice quality impairments [22–24]. Interestingly, recent data support that women could be more susceptible to hoarseness than men because of anatomic, histological, and functional sex-related differences [25]. These sex differences led some authors to consider an LPR diagnosis in women faster than men because of more impressive laryngeal findings [26▪▪]. Moreover, pepsin irritation has been identified as risk factor in the development of many benign lesions of the vocal folds [27] or leukoplakia [28]. Future studies are needed to specify the exact role of LPR in the development of benign lesions [29].

Sign and symptom prevalence

Globus sensation, throat clearing, hoarseness, excess throat mucus, and postnasal drip are the most prevalent symptoms as they are found in at least 75% of patients [24,30,31]. According to the initial analysis of ProGERD Study [32] that remains the largest study conducted on this topic, laryngopharyngeal complaints usually concern 32.8% of GERD patients. In another study, Dore *et al.* [33] identified globus sensation (39%), eructation (26%), cough (24%), and hoarseness (23%) as the most prevalent ENT symptoms in GERD patients. Classical GERD symptoms such as heartburn are usually less prevalent in LPR in comparison with GERD [34]. However, recent findings support that GERD and complications seem to coexist with LPR more often that it was previously assumed [34–37]. This controversial relationship between GERD and LPR led to the development of new clinical tools integrating both GERD and LPR symptoms [35,38]. Regarding findings, posterior commissure hypertrophy, thick endolaryngeal mucus, and laryngeal erythema are the most prevalent LPR signs [24,30,31].

Recent articles support that the prevalence of these symptoms and signs could significantly vary according to sex and age; especially GERD symptoms that are less perceived by elderly patients [25,26▪▪,39,40]. Moreover, some LPR symptoms and signs can be found in healthy individuals. In a cohort of 91 healthy individuals, Chen *et al.* [41▪▪] found that laryngeal erythema, posterior commissure hypertrophy, and diffuse laryngeal edema are the most usual LPR findings met in healthy individuals. In addition, throat clearing and excess throat mucus are both prevalent symptoms of LPR in healthy individuals [41▪▪]. Similar findings were supported by Hicks *et al.* [42] who objectified that 86% of healthy people had LPR findings; certain signs (interarytenoid bar) reaching a prevalence of 70%. These results must be cautiously interpreted because investigators assessed signs of healthy people knowing the clinical state of individuals (healthy) that strongly impacts the reliability of finding assessment [43,44]. According to recent studies [45,46], the use of certain software that assess the erythema intensity of the laryngopharyngeal mucosa could improve the physician endoscopic assessment.

Clinical tools

The majority of clinical researches that have studied LPR symptoms and signs used Reflux Symptoms Index (RSI) and Reflux Finding Score (RFS) as clinical tools [47,48]. Indeed, a recent systematic review exhibited that the 11 symptoms described in RSI and the 8 findings described in RFS are the most frequently assessed clinical outcomes in the evaluation of therapeutic efficiency [1▪▪]. However, the same study and others [16,35,43,49] support that both RSI and RFS are incomplete and do not take into account many LPR symptoms (throat pain, odynophagia, ear pressure, eructation, or halitosis) and findings (vocal fold erythema, leukoplakia,

Table 1. Validated patient-reported outcome questionnaires and laryngopharyngeal reflux finding scores for laryngopharyngeal reflux

			Scale characteristics					
	Objective	**Target and patient characteristics**	**Assessed symptoms/signs**	**Type**	**Item (N)**	**Item response**	**Calculation**	**Subscales**
Patient-reported outcome measures								
TQ [38]	Diagnosis	Patients with globus (pharyngeal symptoms)	GS, PT, DT, DD, EM, VD, IS, CD, TO, HK	VAS	12	Severity: 0–4	Complex calculation	0
	Therapeutic outcome						Total score: 32	
GETS [39]	Diagnosis	Patients with globus (pharyngeal symptoms)	GS, PT, DT, TO, DD, SW, CD, HK, FS	VAS	12	Severity: 0–7	N.P.	3
	Therapeutic outcome						Total score: each item	
RSI [33]	Diagnosis	Suspected or confirmed LPR	VD, GS, TC, EM, CP, DD, PC, CT, HB, RE, CK	VAS	9	Severity: 0–5	Sum of items	0
	Therapeutic outcome						Total score: 45	
LPR-HRQL [40]	Therapeutic outcome of HRQL	Suspected or confirmed LPR	HRQL related to VD, CT, TC, DD	VAS	43	Severity: 0–7 or 0–10	By subscales	5
							Total score: 30-90	
SERQ [41▪▪]	Diagnosis	Pharyngolaryngeal complaints	TC, CT, GS, ST, DD	VAS	9	Severity: 0–4	N.P.	0
	Therapeutic outcome		VD, HB, RE, DC, NC					
LPR-34 [42]	Diagnosis	Suspected or confirmed LPR	TC, GS, EM, PT, VD, DA, FF, PN, TB, BO, HA, RS, HB, DD, PC, IS, WH, VI, BL, RE, BR, CK, NA, HO	VAS	34	Severity: 0–5	N.P.	0
	Therapeutic outcome							
PRSQ [43]	Diagnosis	Suspected LPR	CT, VD, DD, RE, HB	VAS	24	Severity: 0–5	Multiplication of	4
	Therapeutic outcome					Frequency: 0–5	Severity and frequency for each item	
Finding instruments								
RFS [34]	Diagnosis	Suspected LPR	SE, VV, EH, VE, LE, PH, GR, TM	PRI	8	Severity: 0–4	Sum of items	0
	Therapeutic outcome	Confirmed LPR				or 0–2	Total score: 26	
Vaezi	Diagnosis	Uncured LPR	PY, PW, GG, EH	Yes/no	12	Presence: yes/no	Signs prevalence	0
Instrument [44]	Therapeutic outcome		PH, KT, LE, VE, VR, PP, SP, SR				Total score: N.A.	
LRDI [45]	Therapeutic outcome	Suspected LPR	PH, SP, SE, VR, SR, SU, ND, PP, LL, GG, WW	VAS	12	Severity: 0–3	Sum of items	0
							Total score: 36	
LGS [46]	Therapeutic outcome	Suspected LPR	LE, EH, VE, VR	PRI	4	Laryngitis grade: 0–4	–	0
			SE, SU, UC			Each grade is defined		
LRG [47]	Therapeutic outcome	Confirmed LPR	EH, VE, LE, PH, VR, GG, ND, UC, SE	Likert Scale	Signs: 6	Severity: 0–4	Sum of items	Signs scale
					VC wave: 4		Total score: 24+16	VC wave
CPLI [48]	Therapeutic outcome	Suspected LPR	EH, GG, LE, PW	VAS	10	Severity: 0–3	Sum of items	0
			PH, VR, VE				Total score: 30	

AN, anterior pillars erythema/edema; BB, bad breath; BL, belching; BO, bloating; BR, breathing difficulties; CC, chocking; CD, Catarrh down throat; CP, chest pain; CPLI, chronic posterior laryngitis index; CT, troublesome cough; DA, decreased appetite; DC, dry cough; DD, dysphagia; DT, discomfort in throat; EH, laryngeal/arytenoids erythema; EM, excess throat mucous/postnasal drip; F/M, female/male; FF, flatulence; FS, food sticking when swallowing; GETS, Glasgow Edinburgh Throat Scale; GG, interarytenoid granulation and/or granuloma; GS, globus sensation; HA, headache; HB, heartburn; HK, have to keep swallowing; HO, hiccup; IS, indigestion; KT, laryngeal keratosis; LE, laryngeal edema; LGS, laryngoscopic grading scale; LL, leukoplakia; LO, loss light reflect; LPR, laryngopharyngeal reflux; LPR-34, 34-Item Symptom Questionnaire; LPR-HRQ, Laryngopharyngeal Reflux Health-Related Quality of Life; LRDI, laryngopharyngeal reflux disease index; LRG, laryngeal reflux grade; N.A., not available; NA, nausea; NC, nasal congestion; ND, nodules; NN, nocturnal cough; NP, not provided; PC, coughing after you ate/lying down; PH, posterior commissure hypertrophy; PI, mucous pooling in the pyriform sinus; PN, postnasal drip; PO, posterior oropharyngeal wall erythema; PP, polyp/Reinke edema; PRI, predefined item; PRSQ, Pharyngeal Reflux Symptom Questionnaire; PT, pain throat; PW, posterior pharyngeal wall erythema; PY, postpharyngeal cobblestoning; RCT, randomized controlled trial; RE, regurgitations; RFS, reflux finding Score; RS, rush of saliva; RSI, Reflux Symptom Index; SE, subglottic edema/pseudosulcus/stenosis; SERQ, Supraesophageal Reflux Questionnaire; SP, supraglottis edema; SR, supraglottis erythema; SU, subglottic erythema; SW, swelling in the throat; TB, tongue burning; TC, throat clearing; TM, thick endolaryngeal mucus; TO, Throat closing off; TQ, throat questionnaire; TT, tongue tonsil hypertrophy; UC, laryngeal ulcerations; UV, uvula erythema/edema; VAS, visual analog scale; VC, vocal cords; VD, voice disorders; VE, vocal fold edema; VO, vomiting; VR, vocal fold erythema; VV, ventricular obliteration; WH, wheezing; WW, vocal web.

keratosis, posterior pharyngeal wall inflammation, anterior pillars inflammation, coated tongue), which are prevalent in LPR [1▪▪,50,51]. The overuse of RSI and RFS in the assessment of the prevalence of signs and symptoms may correspond to an evaluation bias. Other patient-reported outcomes questionnaires or instruments evaluating clinical LPR findings have been developed and they are described in Table 1 [47,48,52–62]. Nowadays, they are underused in comparison with RSI and RFS. Because of the relationship between GERD, LPR, and some respiratory disease (bronchial responsiveness), the LPR study group of the Young Otolaryngologists of the International Federation of Oto-Rhino-Laryngological Societies (YO-IFOS) has developed a new clinical tool to index symptoms of LPR, GERD, and pulmonary-related disease [38]. Termed the Reflux Symptom Score (RSS), this is in process of validation in English, French and Italian, and is described in Fig. 2.

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 during the last month, 1;2;3;4 = I had 1-2;2-3;3-4;4-5 daily during the last week; 5= complaint occurs daily

	Disorder Frequency	Disorder Severity	Quality of Life impact
Ear Nose and Throat Disorders	Total score:.....	Total score:.....	Total score:.....
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	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Pain during swallowing time	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. 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
5. Clearing your throat	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
6. Sensation of something sticking in the throat	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
7. Excess mucous in the throat or postnasal drip sensation	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
8. Ear pressure/pain (daytime or nigh-time)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
9. Tongue burning	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
10. Other:	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
Abdominal Disorders	Total score:.....	Total score:.....	Total score:.....
1. Heartburn, stomach acid coming up	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
2. Regurgitations of liquids, solid foods or burps	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Abdominal pain	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. Diarrheas	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
5. Constipation	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
6. Indigestion	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
7. Abdominal distension and/or flatus	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
8. Halitosis	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
9. Nausea			
10. Other:	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
Chest/respiratory Disorders	Total score:.....	Total score:.....	Total score:.....
1. Cough after eating or lying down	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
2. Cough (daytime)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Breathing difficulties,breathlessness, or Wheezing	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. Chest pain			
5. Other:	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
Do you think that this questionnaire well assesses your current complaints ?		YES - NO	

FIGURE 2. Reflux symptom score. Reflux symptom score (RSS) is in the process of validation in French, English, and Italian language. Symptoms are assessed within the last month. For each symptom, patient evaluates the occurrence of symptoms (1: once a week; 2: two or three times a week; 3: four or five times a week; 4: six times a week or almost every day; 5: every day), the severity of symptoms (1: symptom is not severe, 5: very severe when it occurs). RSS also assesses the impact of symptoms on quality of life (0: no impact on my quality of life; 5: significant impact on my quality of life). The clinical total score is calculated by the sum of all scores of both severity and frequency of items. The quality of life score is calculated separately. Three subcategories of RSS may be identified according to the affected system: ear, nose, and throat area versus intestinal area versus chest area. From these three sub-scores, future studies could develop thresholds indicating gastroenterological or chest examinations (i.e. gastroscopy, lung function tests, etc.). At the end of the questionnaire, all patients must assess if the questionnaire includes all of the complaints. Additional complaints may be added.

DIAGNOSIS

As there is no gold standard, LPR diagnosis is probably the most controversial aspect of the disease. In 2018, the two most commonly used techniques to make the diagnosis consist of the use of MII impedance-pH metry and, when it is unavailable, the positive response to a well conducted empirical therapeutic trial [63,64]. Over the past few years, pepsin detection is increasingly used as a LPR diagnostic biomarker [27].

Multichannel intraluminal impedance-pH metry

MII impedance-pH metry is, to date, the most reliable examination to perform the diagnosis. According to the significant rate of nonacid reflux [4,65,66], it is important to perform this examination in place of classical pH-metry that does not detect nonacid reflux. However, the use of MII impedance-pH metry is associated with a myriad of LPR diagnostic criteria and probe placements [67], which contribute to the selection of different patient profiles. Overall, the proximal probe is usually placed 1 cm below or 1–3 cm above upper esophageal sphincter and the distal sensor at 5 cm above lower esophageal sphincter. The placement of the proximal probe remains controversial (intraesophageal versus hypopharyngeal) as the movements of pharyngeal probe during the test period may precipitate pseudoreflux episodes secondary to mucosal irritation [68]. With reference to diagnostic criteria, recent data suggest that one or more LPR events in proximal probe should be considered abnormal in patients with LPR symptoms [67] but, to date, there is no international consensus. The difficulty in standardizing diagnostic criteria is related to the fact that normal values for the test could not be definitely established, given the difficulty of carrying out MII impedance-pH metry in a large number of normal volunteers. The main current criticism about MII impedance-pH metry concerns the significant rates of false-positive (7–17%), because of probe placement [69,70], and false-negative because of the lack of reflux episodes during the 24-h period of testing [71]. The false negative problem could be mitigated by the use of 48-h studies. Indeed, a recent study reported better correlation analysis between reflux episodes and symptoms in patients with 48-h MII impedance-pH metry in place of 24-h studies [72]. Moreover, 48-h studies could capture significantly more reflux episodes as compared with 24 h of monitoring alone [72].

Empirical therapeutic trial

Cost and other weaknesses and the unavailability of MII impedance-pH metry in many countries have led to an increasing number of otolaryngologists to base LPR diagnosis on empirical therapeutic trials only [63,64]. This approach is based on the utilization of some clinical scores such as RSI (RSI >13) and RFS (RFS >7) at baseline and the prescription of proton pump inhibitors (PPIs) for a 3-month setup period. Note that initial thresholds can be adapted with regard to sex [26▪▪] and the allergic status [73]. Depending on improvement or not titration of the PPI dose upwards may be proposed for three additional months. LPR diagnosis is only considered if the patient responds after 3 or 6 months of treatment. The diagnosis of nonresponder patients remains uncertain and requires additional examinations (MII impedance-pH metry). Currently, there are many definitions concerning the response to treatment, that is, improvement of 50% of symptom score after treatment [74]; reduction of 5–10 points at RSI [30,75]; and the reduction of both RSI less than 13 and RFS less than 7 after 3 or 6 months of treatment [24,76]. In an overall way, the clinical diagnosis remains difficult as most of the LPR symptoms may be encountered in all conditions affecting laryngopharyngeal mucosa such as allergies, addiction (alcohol, tobacco and drugs), asthma inhalers, environmental irritants, poor vocal hygiene, muscle tension dysphonia; alone or in addition to LPR. Thus, the establishment of LPR diagnosis of empirical therapeutic trial might carefully involve the exclusion of all cofactors or differential diagnoses of LPR [1▪▪]. Moreover, the knowledge of these clinical entities finds all of its importance in case of resistance to PPI treatment. This approach also assumes that acid is the injurious factor when it is known that pepsin alone and bile acids are also inflammatory stimuli. Furthermore, volume escape from the stomach may trigger pharyngeal reflex responses that can be interpreted by some patients as symptomatology and this will not be addressed by PPI therapy and is best managed by blocking or binding agents.

Pepsin and trypsin detection

The analyses of pepsin or trypsin [4] detection are conducted on saliva, or in pharyngeal or laryngeal biopsies (which is more sensitive but invasive) [77,78▪▪]. According to a recent meta-analysis [79], the sensitivity and specificity of salivary pepsin detection are 64 and 68%, respectively. To date, no research studied the trypsin sensitivity and specificity in combination or not with pepsin. In fact, the reliability of pepsin or trypsin detection (sensitivity, specificity, positive and negative predictive values) would be unknown as long as there will be no gold standard. In the 11 studies that assessed the interest of pepsin detection in the LPR diagnosis,

there was an important heterogeneity with regard to the diagnosis method, the exclusion criteria, and the material used for the pepsin detection [79]. The various techniques include Peptest commercial kit (immunoassay), ELISA or western blot; the latter being expensive but providing quantitative analyses. Concerning the sample time, the best time of day for the pepsin collection would be upon waking [80] irrespective of the severity of symptoms because as yet, there is no association between saliva pepsin level and the symptom severity [81].

The place of pepsin and trypsin detection in LPR diagnosis remains unknown. Future investigations have to respond to many unanswered questions about optimal timing for the sampling, location, nature, and threshold values for pepsin testing; whilst taking into consideration that pepsin can easily be endocytosed in mucosal cells, which may lead to erroneous detection of pepsin in the upper aerodigestive tract tissue [17]. Currently, pepsin and trypsin can be used as additional diagnostic methods alongside MII impedance-pH metry in patients with LPR symptoms and signs. The occurrence of symptoms, signs, and positive MII impedance-pH metry, and pepsin or trypsin detection can be considered as the best gold standard that we have.

TREATMENT

PPI efficacy in LPR has long been called into question but a recent meta-analysis/systematic review suggests that PPIs are effective for both LPR signs and symptoms [1▪▪]. In this article, our group found an important heterogeneity between studies according to diagnostic criteria, lack of exclusion criteria, treatment and outcomes that explains the controversy [1▪▪]. The lack of consideration of many signs and symptoms related to reflux is one important factor that may help explain the negative results of some studies that did not observe significant clinical improvement after treatment.

The importance of diet and lifestyle changes has long been underestimated by gastroenterologists and otolaryngologists, although diet is undeniably the first therapeutic step. Indeed, some studies suggest that diet could be sufficient for the treatment of mild LPR [82▪▪]. For moderate-to-severe LPR, the full respect of diet can substantially improve the positive evolution of signs and symptoms in combination with PPIs [10,82▪▪,83,84]. Strict and alkaline diet could also be the therapeutic key for resistant patients to medical treatment [10].

Recent studies underlined the importance of nonacid reflux and the role of trypsin in the pathogenesis of biliary and mixed refluxes [4,66,85]. With regard to these studies, the systematic and exclusive use of PPIs in the LPR therapeutic course can be challenged. It is becoming clear that we must personalize treatment to the patient's reflux profile (diet, lifestyle changes, acid, nonacid, mixed reflux). For example, patients with biliary reflux cannot be treated by PPIs alone as the increase of stomach pH can favor the trypsin activity in the upper aerodigestive tract mucosa, leading to a disease worsening [3]. Thus, as proposed in our therapeutic algorithm (Fig. 3), the first-line LPR treatment combines diet, PPIs, sodium alginate (acid or mixed reflux), magaldrate anhydrous (biliary reflux), in association or not with gastroprokinetic. Alginate drugs make particular sense in case of nonacid, mixed reflux, or in patients with postprandial symptoms. The combination of magaldrate (after the meals) and alginate in bedtime may be useful for many patients. H_2-receptor antagonists (at bedtime) are only recommended as second-line treatment in patients with LPR and GERD, or partial response to PPIs but physicians must keep in mind that these molecules have a relatively short duration of action (4–8 h) [86].

Resistant patients must be primarily assessed for treatment compliance. Indeed, Pisegna *et al.* [87] demonstrated that 62.7% of patients recommended PPIs did not adequately take their treatment, corresponding to the first cause of therapeutic failure. In case of long-term resistance, differential diagnoses of laryngopharyngeal diseases must be carefully reviewed. On the basis of our review of the literature, we established a nonexhaustive list of differential diagnoses of LPR (Table 2) [88–92]. The true resistant patients to the previously cited drugs can benefit from inhibition of transient lower esophageal sphincter relaxations (baclofen) or, in preselected resistant cases (i.e. severe hiatal hernia), fundoplication. Although the results for GERD are excellent, results with LPR patients are less impressive with uncertain laryngeal symptoms improvement [93].

After 3 or 6 months of treatment, it has been suggested that the weaning of patients is successful in approximately 66% [94], although 25–50% patients would have chronic course of the disease [6]. For these patients, the continuation of diet control is important and severe episodes of LPR recurrence can be treated with short-term PPI and alginate (or magaldrate) treatment according to the patient profile. The long-term prescription of PPIs is currently no longer recommended because of long-term side effects of these drugs (i.e. calcium, iron, vitamin malabsorption, renal failure, drug interactions, atrophic gastritis, paediatric growth risks) [95▪▪].

CONCLUSION AND RECOMMENDATIONS

LPR is a complex disease spectrum because of epidemiological, pathophysiological, diagnostic and

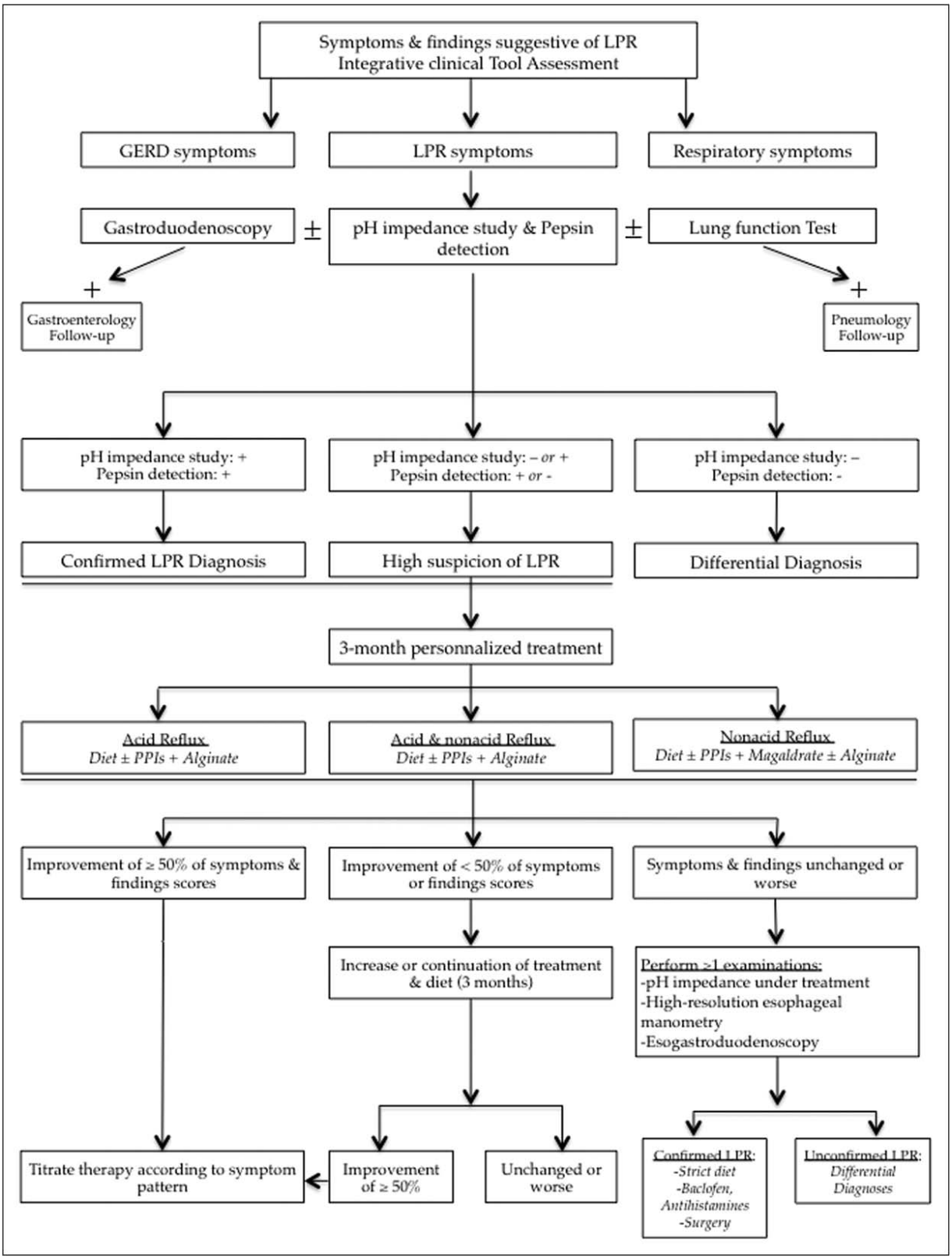

FIGURE 3. Algorithm for assessment and management of suspected or confirmed laryngopharyngeal reflux. The confirmation of LPR is based on positive results at both pepsin detection and pH impedance metry. The lack of reflux in one of these two examinations leads to the suspicion of the diagnosis and the prescription of an empirical treatment. The presence of symptoms related to GERD or pulmonary dysfunction in the fulfilled clinical tools (RSI or RSS or other) may indicate the realization of additional examinations (esogastroduodenoscopy, lung function test, etc.). According to the characteristics of pH impedance

Table 2. Differential diagnoses of laryngopharyngeal reflux

Reported differential diagnoses of symptoms of laryngopharyngeal reflux		
Esophageal disorders	Ear, nose, and throat disorders	Other
Mucosa disorders	*Infections*	*Lung disorders*
Eosinophilic esophagitis	Chronic rhinosinusitis	COPD
Zenker diverticulum	Mycosis	*Psychological*
Esophageal sclerodermia	Recurrent angina	Addiction
Esophageal candidosis	Tuberculosis	(alcohol, tobacco pharyngolaryntidis)
Heterotopic esophageal gastric mucosa	*Rheumatologic/auto-immune disorders*	Stress
Neoplasia	Rheumatic arthritis	Anxiety
Esophageal/sphincter motor disorders	Sjogren's syndrome	Depression
Hypertonicity of upper esophageal sphincter	Laryngeal sarcoidosis	Drugs
Hypertonicity of lower esophageal sphincter	Amyloïdosis	Anticholinergic (salivary hypofunction)
Achalasia	Granulomatosis with polyangiitis	
Esophageal spasm	Fibromyalgia	
Absent peristaltism	Allergy	
Hypercontractile esophagus	*Laryngeal musculoskeletal disorders*	
Gastroparesis	Muscle tension dysphonia	
	Cervical osteophytes	
	Benign or malign tumors	
	Anatomical disorders	
	Size and shape of the epiglottis	
	Tongue tonsil hypertrophy	
	Uvula hypertrophy	
	Retroverted epiglottis	
	(touching the posterior pharyngeal wall)	
	Traumatic	
	Laryngeal fracture	
	Upper aerodigestive tract injury	
	Other	
	Aging voice	
	Allergy	
	Upper aerodigestive tract neoplasia	
	Thyroid disease (nodules, goiter, etc.)	

A nonexhaustive list of differential diagnoses of laryngopharyngeal reflux. COPD, chronic obstructive pulmonary disease.

findings, the treatment is based on diet with or without PPIs with alginate or magaldrate in order to treat acid, nonacid or mixed reflux. The lack of reflux in pH impedance metry or in the case when the patient had no pH impedance metry, empirical treatment is based on diet with or without PPIs with alginate in order to treat acid and a significant part of nonacid refluxes (conjugated biliary salt). Note that patients with low symptoms and signs of LPR can be treated with diet and lifestyle changes. The improvement of at least 50% of LPR signs and symptoms according to the clinical tools used lead to a titration of the treatment with regard to the symptom pattern (patients with postprandial complaints may preferably keep alginate after the meals and reduce PPIs). An improvement of 1–50% of clinical tool scores may lead to the increase or, at least, the continuation of treatment for three additional months. The worsening or the lack of changes of symptoms and signs need additional examinations to better understand the underlying disorder. Patients with LPR and esophageal dysmotility may be treated by baclofen whereas those with a lack of efficiency of PPIs may be treated with strict diet and the use of H_2-receptor antagonists. Surgery is indicated if there is a resistance to all above-mentioned drugs or strict diet. GERD, gastroesophageal reflux disease; LPR, laryngopharyngeal reflux; PPI, proton pump inhibitors.

therapeutic challenges. The main controversy in LPR is still the lack of a reliable tool ensuring definitive diagnosis. As the unstandardized use of MII impedance-pH metry does not assure LPR diagnosis, the development of new better clinical 'instruments-tools' are needed to counteract the flaws of the currently available objective diagnostic tests. It may be that a test battery approach in combination with appropriate symptoms and signs offers the best chance of correctly ascertaining those with reflux-induced disease.

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Conflicts of interest

There are no conflicts of interest.

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