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Evaluation and Management of Laryngopharyngeal Reflux Disease: State of the Art Review

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Abstract

Objective. To review the current literature about the epidemiology, clinical presentation, diagnosis, and treatment of laryngopharyngeal reflux (LPR).

Data Sources. PubMed, Cochrane Library, and Scopus.

Methods. A comprehensive review of the literature on LPR epidemiology, clinical presentation, diagnosis, and treatment was conducted. Using the PRISMA statement, 3 authors selected relevant publications to provide a critical analysis of the literature.

Conclusions. The important heterogeneity across studies in LPR diagnosis continues to make it difficult to summarize a single body of thought. Controversies persist concerning epidemiology, clinical presentation, diagnosis, and treatment. No recent epidemiologic study exists regarding prevalence and incidence with the use of objective diagnostic tools. There is no survey that evaluates the prevalence of symptoms and signs on a large number of patients with confirmed LPR. Regarding diagnosis, an increasing number of authors used multichannel intraluminal impedance–pH monitoring, although there is no consensus regarding standardization of the diagnostic criteria. The efficiency of proton pump inhibitor (PPI) therapy remains poorly demonstrated and misevaluated by incomplete clinical tools that do not take into consideration many symptoms and extralaryngeal findings. Despite the recent advances in knowledge about nonacid LPR, treatment protocols based on PPIs do not seem to have evolved.

Implications for Practice. The development of multichannel intraluminal impedance–pH monitoring and pepsin and bile salt detection should be considered for the establishment of a multiparameter diagnostic approach. LPR treatment should evolve to a more personalized regimen, including diet, PPIs, alginate, and magaldrate according to individual patient characteristics. Multicenter international studies with a standardized protocol could improve scientific knowledge about LPR.

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According to the 2002 position statement of American Academy of Otolaryngology—Head and Neck Surgery, laryngopharyngeal reflux (LPR) refers to the backflow of stomach contents into the laryngopharynx.[1] This definition has recently been considered incomplete because 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. Additionally, the previous definition does not take into account the possible multifactorial origin of symptoms that can be triggered by neuroreflexive signaling and compensatory vagal responses—the indirect effects of LPR.[2] In this regard, this state of the art review defines LPR as an inflammatory condition of the upper aerodigestive tract tissues related to the direct and indirect effects of gastroduodenal content reflux, which may induce morphologic changes in the upper aerodigestive tract.[3]

Since the first publication describing LPR,[4] the number of publications concerning LPR has progressively increased (**Figure 1**). However, many controversies persist regarding epidemiology, diagnosis, and treatment while the number of ambulatory visits increases over the years.[5] Currently, LPR disease is still associated with recurrent symptoms and poor related quality of life[3] that has a significant cost for the patient and society. Thus, the US annual costs for treating LPR and gastroesophageal reflux disease (GERD) are estimated at between $9.3 billion and $50 billion.[6,7] Francis et al found that the mean initial-year direct cost would be $5438 per patient being evaluated for LPR, including consultation, additional examination, and proton pump inhibitor (PPI) consumption.[7] In addition, although the literature concerning empiric therapeutic trials of antacid medication for LPR complaints dates back >15 years, the efficacy of PPIs is still controversial, with only modest superiority over placebo for patients with presumed LPR.[3]

The purpose of this article is to overview the current literature about epidemiology, clinical presentation, diagnosis, and treatment and to shed light on the recent scientific advances on LPR. With a review of this current literature, our LPR study group aims to propose an updated algorithm for LPR management. This review does not apply to children.

Methods

A PubMed, Cochrane Library, and Scopus database search was conducted for relevant peer-reviewed publications in English, Spanish, and French related to epidemiology (incidence and prevalence), clinical presentation, diagnosis, and treatment of LPR. The following terms were used: "reflux," "laryngitis," "laryngopharyngeal," "silent reflux," "extra-esophageal," and "gastroesophageal." We included clinical prospective and retrospective studies, experimental research, meta-analyses, and systematic reviews. Case reports and publications focusing on LPR among children were excluded. From this initial review of the literature, conducted by 3 authors (J.R.L., M.R.B., S.S.), articles were selected for inclusion in the final review if they focused on epidemiology, clinical presentation, diagnosis, and treatment of LPR. Authors had to report inclusion and exclusion criteria; diagnostic, incidence, and prevalence methods; therapeutic outcomes (eg, clinical tools, list of symptoms or signs); and the treatment regimen. Article selection by PRISMA criteria is summarized in the flowchart in **Figure 2**. Critical analysis of this literature was then performed focusing on incidence and prevalence, clinical presentation, diagnosis, and treatment. Implications for practice were then summarized. Ethics committee approval was not required for this review.

Discussion

Incidence and Prevalence

In 1991, Jamie Koufman estimated the LPR incidence at 10% of outpatients presenting to otolaryngology clinics with extraesophageal manifestations of GERD.[4] In this cohort, 62% had abnormal esophageal pH studies, and 30% had documented reflux into the pharynx. This study was perhaps the first important research article differentiating LPR from GERD, but there was no epidemiologic survey performed in general ear, nose, and throat consultation.[4] Gaynor estimated that 1% of patients visiting general practitioners had symptoms suggestive of LPR, although no testing was done to confirm the LPR diagnosis.[8] In 2007, Connor et al assessed the LPR prevalence in the Wisconsin area with a screening LPR questionnaire, and they concluded that about 26.2% of subjects had both laryngeal symptoms and concomitant GERD.[9]

Several more recent studies used the Reflux Symptom Index (RSI) to estimate LPR prevalence in various populations with different thresholds. Chen et al estimated the LPR prevalence (RSI >13)[10] at 18.8% of the Chinese population.[11] In similar studies, Spantideas et al and Kamani et al found that 5% (RSI ≥13) and 30% (RSI >10) of Greek and British populations had LPR symptoms.[12,13] In each of these 4 studies, authors did not perform any additional clinical or objective examinations to confirm reflux diagnosis, making it possible that RSI scores were due to chronic inflammation of other etiology.[3,14,15]

In 2000, Koufman et al performed dual-probe pH monitoring in 113 patients with dysphonia. In this group, 69% of patients had symptoms and findings of LPR, and 73% had abnormal reflux testing.[16] When those studies were interpreted, it was obvious that the authors focused only on acid reflux and did not take into consideration nonacid/mixed reflux. One of the most fundamental principles in epidemiology is that to precisely assess incidence and prevalence of a disease, researchers must have a gold standard diagnosis. Nowadays, there is no gold standard ensuring LPR diagnosis, although technology is evolving—new studies are measuring

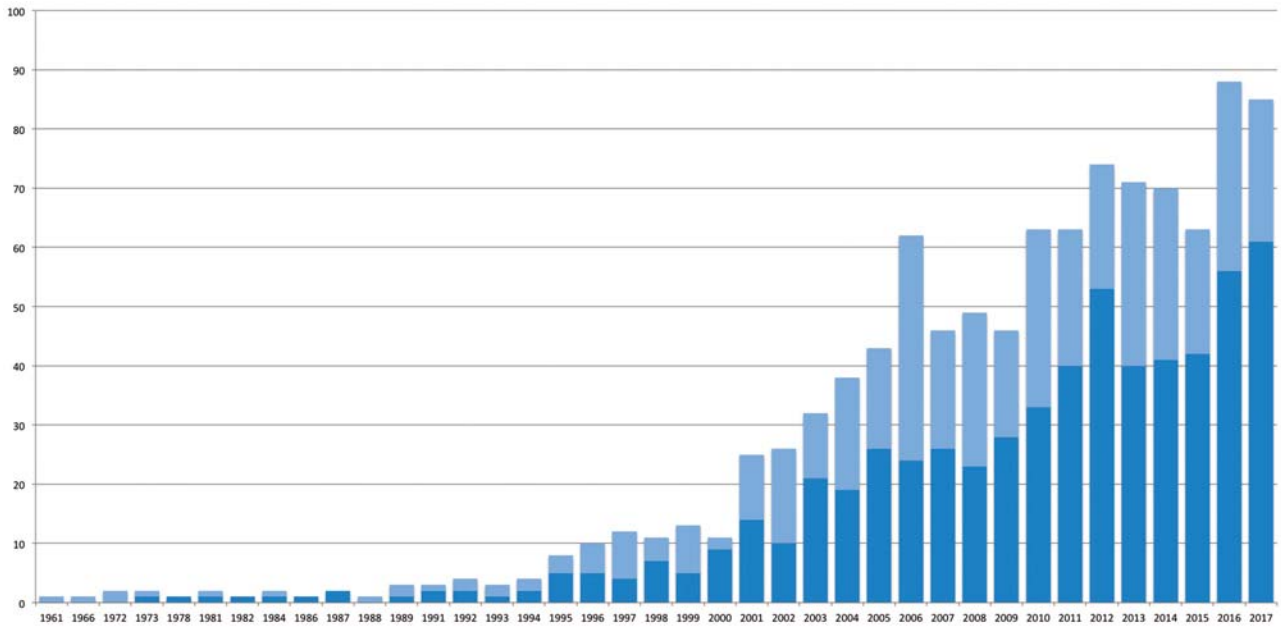

Figure 1. Evolution of published papers about laryngopharyngeal reflux over the past decades. This graph shows the total number of clinical studies (dark blue) and the total number of publications (dark and light blue) performed about laryngopharyngeal reflux according to the year.

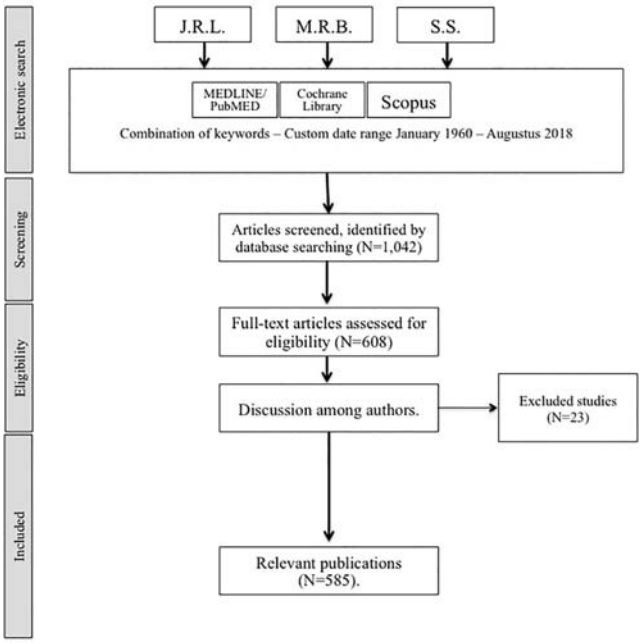

Figure 2. PRISMA flowchart. Since 1961, a total of 1042 publications were identified (608 clinical studies with patient data). Twenty-three studies were excluded because of a lack of a full manuscript in English, Spanish, or French. Finally, 585 were included to write this systematic review.

both nonacid and mixed reflux as each can cause LPR,[17,18] and comparative studies are showing how pH metry alone might underestimate reflux diagnoses.[19]

In summary, regarding the nonspecificity of symptoms, the lack of a gold standard, and the use of multichannel intraluminal impedance–pH monitoring (MII-pH) for the diagnosis, it is still difficult to establish LPR incidence and prevalence. To more fully comprehend LPR prevalence, consideration of the overlap among LPR signs, symptoms, and positive MII-pH might best identify patients with LPR.

Clinical Presentation

Pathogenesis. The reflux of pepsin, bile salts, 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.[20-22] Accumulation of sticky mucus induces postnasal drip and globus sensation, throat clearing, and cough. Certain anatomic findings, such as granuloma, contact between epiglottis and hypertrophied lingual tonsils, and oropharyngeal posterior wall, may also lead to globus sensation. Globus sensation may also be neurogenic. The inflammation of soft palate or rhinopharyngeal mucosa may be associated with postnasal drip. Dysphonia could be caused by macro- and microscopic mucosal changes that may induce modifications of biomechanical properties of the vocal folds, contributing to the development of chronic lesions of the vocal folds.[22-25]

Indirect injury from vagally mediated reflexes may also favor the development of LPR symptoms, as the stimulation of gastroduodenal content into the low esophagus may stimulate the mucosa chemoreceptors, leading to laryngeal mucus secretion, cough, globus sensation, and throat clearing.[2] Dysphagia, odynophagia, ear pressure, and throat pain may also develop throughout the chronic inflammatory reaction of the mucosa.[26] Despite chronic LPR disease, many patients have acute episodes of reflux through the internalization/externalization of pepsin,[27] which can

exacerbate these symptoms, leading to the description of the ''chronic course'' of disease. The etiology of symptoms may be multifactorial for patients with concomitant LPR and obstructive sleep apnea syndrome, based on recent data that supported a strong association between obstructive sleep apnea syndrome severity and reflux symptoms.[28]

Symptoms and Signs. In practice, the prevalence of the LPR symptoms described so far was extensively studied in many large cohort studies (**Table 1**).[4,29-40] The most prevalent LPR symptoms are globus sensation, throat clearing, hoarseness, excess throat mucus, and postnasal drip. However, reported prevalence of these complaints varies among studies because of heterogeneity in inclusion/exclusion criteria, diagnostic approaches, and determination/definition of clinical symptoms. The inclusion of patients with active allergy,[29] patients with chronic rhinosinusitis,[30] smokers,[29,30,38] and alcoholics[38] may bias the LPR symptom assessment because these conditions may be associated with similar complaints. Additionally, the prevalence of LPR symptoms could significantly vary according to sex and age, especially as GERD symptoms are less perceived by elderly patients.[41-44]

The common LPR findings are posterior commissure hypertrophy, laryngeal/arytenoid inflammation, and endolaryngeal mucus (**Table 2**).[29-31,33,38] However, these studies are characterized by the same heterogeneity as those focusing on symptoms. The common characteristic of the 2 largest studies is the use of the Reflux Finding Score (RFS),[45] excluding some other LPR signs not described in the RFS. Even with common ''language'' for findings suggested by the RFS, however, limitations relate to whether findings are assessed in a blinded or nonblinded fashion, possibly affecting reliability.[46,47] Interestingly, a recent study suggested that LPR findings could vary according to type of reflux and patient characteristics.[18] In the same way, women with LPR could have lower laryngeal signs (RFS) than men, supporting the use of a sex-related cutoff in LPR diagnosis based on the RFS.[41]

Relationship between LPR and GERD. The relationship between LPR and GERD is controversial, although they share common physiologic mechanisms, but many studies supported a relationship between both conditions more often than previously assumed. It is accepted that $\leq$50% of patients with LPR have GERD.[29,48] For 3 decades, the overall trend was to consider these 2 conditions as different diseases,[49] but many studies supported a relationship more often than previously assumed. Through the ProGERD Study,[48] Jaspersen et al showed that laryngopharyngeal complaints were present among 32.8% of patients with GERD. Dore et al found that 39% of patients with GERD had encountered globus sensation with a significant rate of eructation (26%), cough (24%), and hoarseness (23%).[32] Erosive esophagitis was found in almost 50% of patients with GERD,[50] while for LPR, only 10% to 30% of patients had esophagitis, with a low proportion of patients (<10%) having Barrett's metaplasia.[51-55] Lai et al showed that 24% of patients with erosive esophagitis had complaints and findings suggestive of LPR.[56] In a cohort of 1383 patients with GERD, Groome et al demonstrated a correlation between the severity of GERD and the development of LPR. Patients with Barrett's metaplasia had, however, a higher rate of LPR than those with mild erosive esophagitis.[57,58]

Clinical Tools. Some patient-reported outcome measures and instruments evaluating the clinical findings were developed over the past 20 years for the diagnosis and the evaluation of treatment effectiveness (**Tables 3** and **4**).[40,45,52,59-70] Among these, the RSI[60] and RFS[45] are the most popular clinical LPR tools, and the RSI has been adapted and validated in many languages.[10,71-76] Due to the popularity of the RSI and RFS, the 11 symptoms and the 8 findings described in them are the most frequently assessed clinical therapeutic outcomes.[3] However, these tools have many weaknesses.[3,59,77]

Regarding the RSI, LPR symptoms are usually nonspecific, and they can be found among subjects without reflux. Chen et al observed a significant rate of throat clearing, excess throat mucus or postnasal drip, and globus sensation among healthy subjects.[78] This point is important because the RSI does not take into consideration many LPR symptoms—namely, throat pain, odynophagia, ear pressure, eructation, and halitosis.[3,79,80] Second, the RSI provides a severity evaluation of LPR complaints with a visual analog scale but does not take into consideration the symptom frequency. The only evaluation of symptom severity with a visual analog scale is subjective and involves some sociocultural factors. Third, some symptoms described in the RSI (heartburn, chest pain, regurgitations, and indigestion) are pooled into 1 item, leading to confusion in the assessment of these complaints. With regard to these criticisms, our group recently developed a new patient-reported outcome questionnaire (Reflux Symptom Score) that includes evaluations of LPR and GERD symptom frequency, severity, and impact of quality of life, with a clear definition of each rating item.[81]

Regarding findings, 80% of healthy subjects could have $\geq$1 signs of laryngopharyngeal irritation, including laryngeal erythema, posterior commissure hypertrophy, and diffuse laryngeal edema.[66,78,82] The RFS does not take into consideration many LPR findings, including vocal fold erythema, leukoplakia, posterior pharyngeal wall inflammation, anterior pillars inflammation, and coated tongue.[3,79,80,83] Some LPR signs are described in **Figure 3**. Second, the RFS allows a subjective evaluation of some signs without clear definition of the rating, which can be a factor explaining the low interreliability among judges.[46,47,84] This observation can be attributed to the nonspecificity of LPR signs and the subjective procedure of evaluation of some items of the RFS (mild, moderate, or severe score of a finding). In that respect, future instruments could include findings of all upper aerodigestive tract mucosa related to LPR, and the meaning of each item should be closely defined to improve the interrater reliability of physicians. The evaluation of some signs with a visual analog scale should be avoided. Moreover, because some

Table 1. Prevalence of LPR Symptoms according to the Larger Studies (N >100 Patients with LPR).[a]

Publication	Patients with LPR, n	Diagnosis Criteria	Clinical Instruments	Assessed Symptoms	Prevalent Symptoms	Symptoms, %
Habermann (2012)[29]	1044 suspected	Reflux Symptom Index >9, Reflux Finding Score >7	Reflux Symptom Index	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	(1) Globus sensation. (2) Throat clearing. (3) Excess throat mucus	—
Lee (2011)[30]	455 suspected	Symptoms and signs	Reflux Symptom Index	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	(1) Globus sensation. (2) Throat clearing. (3) Hoarseness	89, 82, 79
Chappity (2014)[31]	234 suspected	Reflux Symptom Index >13	Reflux Symptom Index	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	(1) Globus sensation. (2) Pain throat. (3) Throat clearing	70, 54, 47
Dore (2007)[32]	226 suspected	Laryngeal symptoms	Unvalidated clinical tool	HB, RE, DD, OD, SA, CP, VD, GS, TC, EM, CK, EE, HO, NA	(1) Globus sensation. (2) Eructation. (3) Cough	39, 26, 24
Koufman (1991)[4]	225 confirmed	Symptoms and signs, pH monitoring	—	GS, DD, CT, VD, HB, RE	(1) Dysphonia. (2) Cough. (3) Globus sensation	71, 51, 47
Youssef (2010)[33]	212 confirmed	Symptoms and signs, pH monitoring	—	CT, TC, VD, BT, GS	(1) Cough. (2) Globus sensation. (3) Throat clearing	50, 46, 37
Zalvan (2017)[34]	188 suspected	Reflux Symptom Index >10	Reflux Symptom Index	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	(1) Dysphonia. (2) Dysphagia. (3) Cough	34, 34, 32
Lee (2014)[35]	180 suspected	Symptoms and signs	Reflux Symptom Index	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	(1) Dysphonia. (2) Cough. (3) Throat clearing	—
Drinnan (2015)[36]	177 suspected		Reflux Symptom Index	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	(1) Throat clearing. (2) Dysphonia. (3) Globus sensation	45, 40, 37
Vaezi (2006)[37]	145 suspected and confirmed	Symptoms, chronic posterior laryngitis ≥5, pH monitoring (not all)	Unvalidated clinical tool	TC, CT, VD, PT, GS	(1) Throat clearing. (2) Dysphonia. (3) Cough	50, 20, 13
Hanson (1995)[38]	141 suspected	Symptoms and signs	—	VD, PT, PC, TC, GS, CT	(1) Sore throat. (2) Dysphonia. (3) Postnasal drip	—
Nunes (2016)[39]	126 suspected	Symptoms and signs	Reflux Symptom Index	VD, GS, TC, EM, DD, PC, CT, HB, CP, PS, CK	(1) Cough. (2) Globus sensation. (3) Dysphonia	40, 21, 20
Andersson (2010)[40]	102 confirmed	Reflux Symptom Index >13, pH monitoring	Pharyngeal Reflux Symptom Questionnaire	VD, CT, DD, HB, CP GS, PT, RE, EM	(1) Cough. (2) Throat clearing. (3) Globus sensation	91, 89, 88

Abbreviations: BT, bad taste; CK, choking; CP, chest pain; CT, troublesome cough; DD, dysphagia; EE, eructation; EM, excess throat mucous/postnasal drip; GS, globus sensation; HB, heartburn; HO, hiccup; LPR, laryngopharyngeal reflux; NA, nausea; OD, odynophagia; PC, coughing after you ate/lying down; PS, pyrosis/stomach acid coming up; PT, pain throat; RE, regurgitations; SA, sialorrhea; TC, throat clearing; VD, voice disorders.

[a]The prevalence of LPR symptoms among patients with suspected or confirmed LPR. Studies focusing on patients with LPR who were resistant to medical treatment or patients with hoarseness were not considered.

Table 2. Prevalence of LPR Signs according to the Larger Studies (N >100 Patients with LPR).[a]

Publications	Patients with LPR, n	Diagnosis Criteria	Finding Tools	Findings	Prevalent Findings	Findings, %
Habermann (2012)[29]	1044 suspected	Reflux Symptom Index >9, Reflux Finding Score >7	Reflux Finding Score	SE, VV, EH, VE, LE, PH, GG, TM	(1) Posterior commissure hypertrophy. (2) Laryngeal erythema. (3) Thick endolaryngeal mucus	—
Lee (2011)[30]	455 suspected	Symptoms and signs	Reflux Finding Score	SE, VV, EH, VE, LE, PH, GG, TM	(1) Posterior commissure hypertrophy. (2) Vocal fold edema. (3) Laryngeal erythema	89, 80, 79
Chappity (2014)[31]	234 suspected	Reflux Symptom Index >13	—	DT, EH, LE, NC, PY, PW, VR, PH	(1) Dull tympanic membrane. (2) Arytenoid inflammation. (3) Posterior pharyngeal wall inflammation	45, 44, 43
Youssef (2010)[33]	212 confirmed	Symptoms and signs, pH monitoring	—	LE, EM, UC, GG	(1) Arytenoid erythema. (2) Endolaryngeal mucus. (3) Laryngeal ulcer	55, 28, 11
Hanson (1995)[38]	141 suspected	Symptoms and signs	—	EH, LE, PH, PW, GG, TM, KT	(1) Laryngeal erythema. (2) Hypopharyngeal wall erythema. (3) Laryngeal and hypopharyngeal edema	—

Abbreviations: DT, dull tympanic membrane; EH, laryngeal/arytenoids erythema; EM, excess throat mucous/postnasal drip; GG, granuloma/granulations (posterior commissure); KT, laryngeal keratosis; LE, laryngeal edema; LPR, laryngopharyngeal reflux; NC, nasal congestion; PH, posterior commissure hypertrophy; PW, posterior pharyngeal wall erythema; PY, postpharyngeal cobblestoning; SE, subglottic edema; TM, thick endolaryngeal mucous; UC, laryngeal ulcerations; VE, vocal folds edema; VR, vocal folds erythema; VV, ventricular obliteration.

[a]The prevalence of LPR findings among patients with suspected or confirmed LPR. Studies focusing on patients with LPR who were resistant to medical treatment or patients with hoarseness were not considered.

Table 3. Validated Patient-Reported Outcome Measures.

Patient-Reported Outcome Measures	Objective	Target and Patient Characteristics	Patients for Validation	Users or Studies, n	Scale Characteristics					
					Assessed Symptoms	Type	Item, n	Item Response	Calculation	Subscales
Throat Questionnaire (Wilson[61])	Diagnosis, therapeutic outcome	Patients with globus (pharyngeal symptoms)	89 suspected LPR	0-5	GS, PT, DT, DD, EM, VD, IS, CD, TO, HK	VAS	12	Severity: 0-4	Complex calculation. Total score: 32	0
Glasgow Edinburgh Throat Scale (Deary[62])	Diagnosis, therapeutic outcome	Patients with globus (pharyngeal symptoms)	105 globus	5-25	GS, PT, DT, TO, DD, SW, CD, HK, FS	VAS	12	Severity: 0-7	Not provided. Total score: each item	3
Reflux Symptom Index (Belafsky[60])	Diagnosis, therapeutic outcome	Suspected or confirmed LPR	25 confirmed LPR	50-100	VD, GS, TC, EM, CP, DD, PC, CT, HB, RE, CK	VAS	9	Severity: 0-5	Sum of items. Total score: 45	0
Laryngopharyngeal HRQL (Carrau[63])	Therapeutic outcome of HRQL	Suspected or confirmed LPR	117 suspected LPR	0-5	HRQL related to VD, CT, TC, DD	VAS	43	Severity: 0-7 or 0-10	By subscales. Total score: 30-90	5
Supraesophageal Reflux Questionnaire (Dauer[64])	Diagnosis, therapeutic outcome	Pharyngolaryngeal complaints	985 suspected LPR	0-5	TC, CT, GS, ST, DD, VD, HB, RE, DC, NC	VAS	9	Severity: 0-4	Not provided	0
Laryngopharyngeal Reflux-34 (Papakonstantinou[65])	Diagnosis, therapeutic outcome	Suspected or confirmed LPR	62 suspected LPR	0-5	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	Not provided	0
Pharyngeal Reflux Symptom Questionnaire (Andersson[40])	Diagnosis, therapeutic outcome	Suspected LPR	228 suspected LPR	0-5	CT, VD, DD, RE, HB	VAS	24	Severity: 0-5. Frequency: 0-5	Multiplication of severity and frequency for each item	4

Abbreviations: BL, belching; BO, bloating; BR, breathing difficulties; CD, Catarrh down throat; CK, choking; CP, chest pain; CT, troublesome cough; DA, decreased appetite; DC, dry cough; DD, dysphagia; DT, discomfort in throat; EM, endolaryngeal mucus; FF, flatulence; FS, food sticking when swallowing; GS, globus sensation; HA, headache; HB, heartburn; HK, have to keep swallowing; HO, hiccup; HRQL, health-related quality of life; IS, indigestion; LPR, laryngopharyngeal reflux; NA, nausea; NC, nasal congestion; PC, coughing after you ate/lying down; PN, postnasal drip; PT, pain throat; RE, regurgitations; RS, rush of saliva; ST, sore throat; SW, swelling in the throat; TB, tongue burning; TC, throat clearing; TO, throat closing off; VAS, visual analog scale; VD, voice disorders; VI, vomiting; WH, wheezing.

Table 4. Validated Instruments Evaluating the Clinical Findings.

					Scale Characteristics					
Finding Instruments	Objective	Target and Patient Characteristics	Patients for Validation	Users or Studies, n	Assessed Signs	Type	Items, n	Item Response	Calculation	Subscales
Reflux Finding Score[45]	Diagnosis, therapeutic outcome	Suspected LPR, confirmed LPR	40 confirmed LPR	25-50	SE, VV, EH, VE, LE, PH, GR, TM	Predefined item	8	Severity: 0-4 or 0-2	Sum of items. Total score: 26	0
Vaezi Instrument[66]	Diagnosis, therapeutic outcome	Uncured LPR	72 suspected LPR	0-5	PY, PW, GG, EH, PH, KT, LE, VE, VR, PP, SP, SR	Yes/no	12	Presence: yes/no	Signs prevalence. Total score: NA	0
Laryngopharyngeal Reflux Disease Index[67]	Therapeutic outcome	Suspected LPR	Suspected LPR, N = NA	0-5	PH, SP, SE, VR, SR, SU, ND, PP, LL, GG, WW	VAS	12	Severity: 0-3	Sum of items. Total score: 36	0
Laryngoscopic Grading Scale[68]		Suspected LPR	20 suspected LPR	0-5	LE, EH, VE, VR, SE, SU, UC	Predefined item	4	Laryngitis grade: 0-4. Each grade is defined	—	0
Laryngeal Reflux Grade[69]	Therapeutic outcome	Confirmed LPR	42 LPR	0-5	EH, VE, LE, PH, VR, GG, ND, UC, SE	VAS	Signs: 6. VC wave: 4	Severity: 0-4	Sum of items. Total score: 24+16	Signs scale. VC wave
Chronic Posterior Laryngitis Index[70]	Therapeutic outcome	Suspected LPR	145 suspected	0-5	EH, GG, LE, PW, PH, VR, VE	VAS	10	Severity: 0-3	Sum of items. Total score: 30	0

Abbreviations: +, criterion met; EH, laryngeal/arytenoids erythema; GG, interarytenoid granulation and/or granuloma; GR, laryngeal granulation/granuloma; KT, laryngeal keratosis; LE, laryngeal edema; LL, leukoplakia; LPR, laryngopharyngeal reflux; NA, not available; ND, nodules; PH, posterior commissure hypertrophy; PP, polyp/Reinke edema; PW, posterior pharyngeal wall erythema; PY, postpharyngeal cobblestoning; SE, subglottic edema/pseudosulcus/stenosis; SP, supraglottis edema; SR, supraglottis erythema; SU, subglottic erythema; TM, thick endolaryngeal mucus; UC, laryngeal ulcerations; VAS, visual analog scale; VC, vocal cords; VE, vocal fold edema; VR, vocal fold erythema; VV, ventricular obliteration; WW, vocal web.

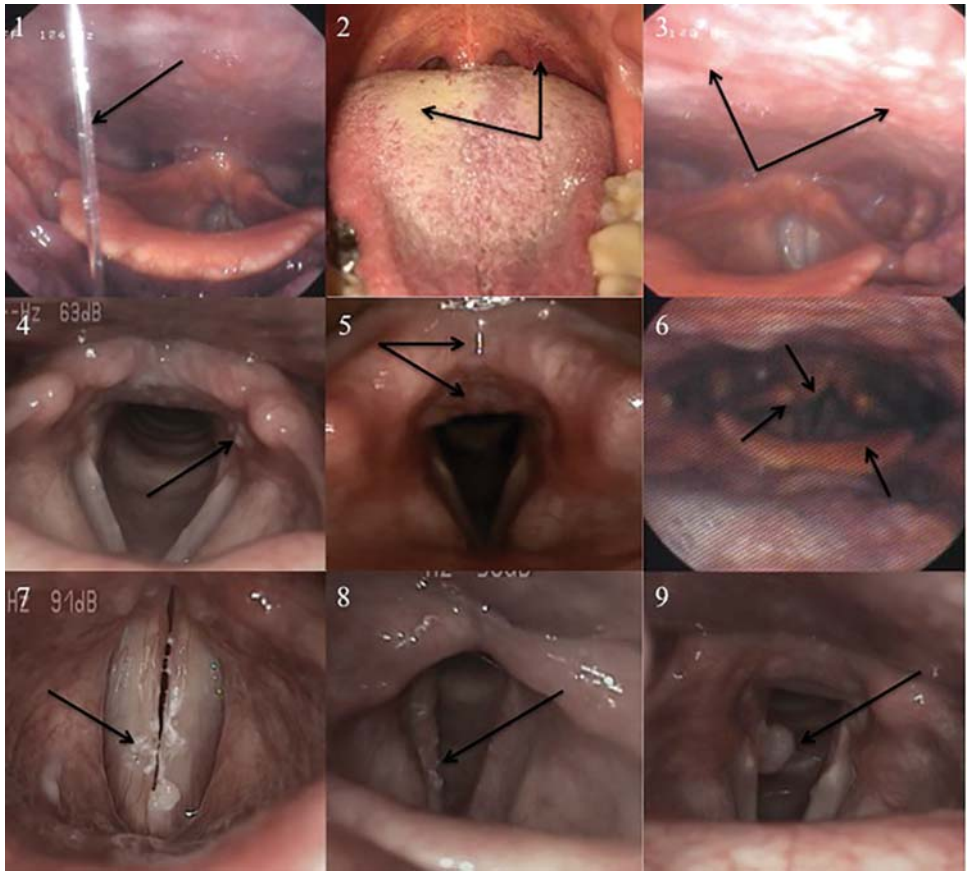

Figure 3. Arrows show prevalent findings associated with laryngopharyngeal reflux: sticky secretions (1), erythema of the anterior pillars and coated tongue (2), nodularity of the posterior pharyngeal wall (3), laryngeal keratosis (4), posterior commissure hypertrophy and interarytenoid granulation (5), diffuse laryngeal erythema (6), endolaryngeal mucus (7), laryngeal ulcerations (8), and granuloma (9). These findings are nonspecific and should be considered in a complete finding score.

findings could probably require more time to change, it could be interesting to follow patients with LPR over longer follow-up periods.

In summary, the most prevalent complaints and findings found in the larger cohorts of patients with suspected LPR are also the most prevalent complaints and findings found among healthy subjects, confirming the nonspecificity of LPR symptoms and signs and the need to combine symptoms and findings with objective examinations for the diagnosis. From an epidemiologic standpoint, the lack of consideration of some clinical outcomes of a disease may undeniably affect the establishment of a clinical diagnosis and the evaluation of therapeutic efficiency.[85] This fact has to lead to the use of complete clinical instruments at baseline and throughout treatment to precisely assess the evolution of laryngeal and extralaryngeal symptoms and signs. Furthermore, in an attempt to minimize subjectivity in the reflux finding assessment,[46] software was recently developed to improve the assessment of the erythema intensity of the laryngopharyngeal mucosa.[86-88]

Objective Testing

MII-pH Monitoring. MII is able to detect esophageal bolus movement by measuring changes in electrical resistance, and it is associated with pH monitoring. The single-use 2-mm-width MII-pH catheter contains ring electrodes that are usually positioned 3, 5, 7, 9, 15, and 17 cm from the tip and combined with at least 1 pH electrode at the tip. Intraesophageal/pharyngeal content transit (liquid and air) is detected as sequential changes in impedance along the catheter. MII-pH is the most reliable means to precisely diagnose of acid, nonacid, or mixed reflux. Addition of impedance testing improves the sensitivity (70%-80%) and the false-negative rate (20%-50%) of classical pH monitoring, which is unable to detect nonacid reflux or some aerosolized molecules.[19,50,89] The replacement of pH metry by MII-pH makes sense regarding the significant rate of nonacid LPR that can be resistant to PPIs.[17,18,90,91]

However, MII-pH has several limitations. First, the number and characteristics of reflux episodes may vary from day to day, and the results can be associated with false-positive and false-negative rates.[92] A lack of reflux episodes during the 24-hour testing period does not necessarily signify that the patient does not have LPR; it only indicates that there were no reflux episodes during the test period.[93] Thus, some authors recently recommended the use of 48-hour studies to mitigate the false-negative problem.[94] The patient's diet the day of the examination also has a

significant impact on the results.[95,96] Second, the results of pH study probes may be inaccurate if drying of the proximal sensor leads to inaccurate measurement, resulting in pseudo-reflux.[96,97] Third, MII-pH does not systematically predict LPR symptom response throughout the PPI therapeutic trial.[50,98-100] Finally, there is no standardization of interpretation for results at the proximal sensor—in the existing literature concerning MII-pH and reflux, there is a myriad of diagnostic criteria (**Table 5**).*

According to our review, some physicians still consider criteria based on pH results without regard for impedance events,[90,104,117,120] and others use the criteria for GERD developed for measurement at the distal pH sensor.[92,107] In fact, only a few authors used 1 or several pH drops or impedance events at the proximal probe irrespective to the absolute pH at that time.[18,121] Further difficulty in standardization of diagnostic criteria is partly related to the fact that normative values for the test are incompletely established, given the difficulty of carrying out MII-pH monitoring in a large number of normal volunteers. Other barriers to the use of MII-pH are the cost, the inconvenience to the patient, and the unavailability in all centers. However, in the absence of a gold standard for diagnosis, current research on diagnosis, treatment, and other issues concerning LPR remains limited by an inability for different articles to be discussing the same population—each different set of diagnostic criteria likely leads the population from one study to be different in potentially meaningful ways from the populations of other studies.

Oropharyngeal pH Monitoring. Among various approaches that are designed to address some of the limitations of pH metry for LPR, one is a novel pH device (Restech; Respiratory Technology Corp, San Diego, California), which was developed for purposeful hypopharyngeal rather than proximal esophageal measurement. It consists of a single hypopharyngeal probe designed to measure pH of aerosolized droplets, and it is not subject to drying artifacts, which can occur if traditional esophageal probes are positioned above the upper esophageal sphincter. A few studies have since used oropharyngeal pH metry for LPR diagnosis in the place of MII-pH. Studies that used pharyngeal and dual pH esophageal probes simultaneously showed that the oropharyngeal probe does reliably capture reflux episodes, which moved proximally from esophagus to pharynx.[92,122-124] Thus, Becker et al showed that oropharyngeal pH metry detected only 11% of reflux episodes detected by MII-pH.[92] Studies that compared the ability of pharyngeal versus esophageal pH monitoring to predict symptom response to PPI treatment among patients with presumed LPR suggested that the oropharyngeal probe may have higher positive predictive capability than that of esophageal measurement, but these findings are based on low numbers of patients and remain preliminary.[92] As with MII-pH metry, there is no consensus about the diagnostic criteria, although the majority of studies used similar criteria: Ryan score >9.4 (upright) or >6.8 (supine).[125-131]

Empirical Therapeutic Trial. Another tool used for ''diagnosis'' is an empiric trial of antacid medication.[132,133] Formal application of this approach involves the utilization of some clinical scores for the diagnosis (typically RSI >13 and/or RFS >7), followed by treatment with dietary recommendations and PPIs for 3 months and then reassessment of clinical status. At the time of reassessment, many definitions of response are considered positive for assignment of a reflux diagnosis. These include a 50% improvement of symptoms score after treatment,[134] both a ≥3-point RFS reduction and a ≥5-point or ≥6-point RSI reduction,[34] or a reduction of scores to RSI <13 and RFS <7 after 3 or 6 months of treatment.[135-137] In many cases, authors did not define the criteria of improvement.[108,132,133] Overall, many authors defined response on the basis of only symptoms and not signs.

There are several limitations in the use of response to empiric treatment to retroactively assign reflux diagnoses. One is that confounding etiologies, such as allergy, might drive patient complaints[138] and influence degree of improvement. A second issue is that response to PPIs does not tell the treating physician what to do with nonresponders—while it is possible that those with persistent cough, globus sensation, throat clearing, and/or other presumed LPR complaints may not actually have reflux if they do not respond to empiric treatment, it is also possible that refractory reflux or nonacid reflux may be present; this would be identified on MII-pH but cannot be excluded on the basis of empiric treatment. Finally, a critical drawback of empiric treatment is the nonspecific nature of the vague laryngopharyngeal complaints, which often lead physicians to presume LPR. These complaints may instead be related to self-limited laryngopharyngeal inflammation from overuse, dryness, upper respiratory tract infection, habituated behavioral trauma, allergy, and the like, and trials often show no benefit from PPIs over placebo in the treatment of patients with presumed LPR.[3,139] In this way, Ross et al found that patients with suspected LPR had increased abnormal perceptual voice characteristics (eg, musculoskeletal tension, hard glottal attack, glottal fry, restricted tone placement, and hoarseness) as compared with the controls, which can raise the LPR-attributed symptoms.[140] If these patients without LPR would have experienced symptomatic improvement over time in the absence of PPIs, then results of an empiric PPI trial might subject these patients to unnecessary medication and assign reflux diagnosis falsely. Nowadays, it is recommended to carefully exclude many confounding factors associated with laryngopharyngeal complaints (chronic laryngopharyngitis due to tobacco, alcohol, allergy, infections, asthma inhalers, environmental irritants, poor vocal hygiene, muscle tension dysphonia, etc).[3]

Pepsin and Bile Salt Detection. The detection of pepsin, bile salts, and probably trypsin on saliva and pharyngeal or laryngeal mucosa is a promising diagnostic approach.[141] A

*References 18, 53, 84, 90, 92, 98, 101-121

Table 5. Diagnostic Criteria of Multichannel Intraluminal Impedance–pH Monitoring and Probe Placements.[a]

References	Diagnostic criteria	Probe Placement
Jiang (2011)[102]	NP	Proximal: 0.5 cm above UES. Distal: 5 cm above LES
Wang (2011)[103]	Total acid exposure time pH <4 >4% of time	Proximal: 0-1 cm above UES. Distal: 3-5 cm above LES
Wang (2012)[104]	Total acid exposure time pH <4 >4% of time	Proximal: 0-1 cm above UES. Distal: 3-5 cm above LES
de Bortolini (2012)[105]	Distal acid exposure >4.2% of time	Proximal: 17 cm above LES. Distal: 5 cm above LES
Beckers (2012)[92]	Total acid exposure time pH <4 >4% of time or number of reflux episode >73	Proximal: NP. Distal: 5 cm above LES
Xiao (2012)[106]	≥1 proximal events	Proximal: 0.5 cm above UES. Distal: 5 cm above LES
Wang (2011)[107]	Total acid exposure time pH <4 >4% of time	Proximal: 0-1 cm above UES. Distal: 3-5 cm above LES
Wan (2014)[108]	≥3 LPR pharyngeal episodes or proximal acid exposure time >1% or impedance proximal acid exposure ≥4	Proximal probe: esophagus 2 cm below UES. Distal probe: 20 cm below the proximal probe
Jetté (2014)[84]	Proximal probe: decrease in pH by >2 units within 30 s to a value <4 units	Proximal probe: 0.5-1 cm above UES. Distal probe: 5 cm above LES
Mazzoleni (2014)[109]	Number of reflux episode >73 or distal acid exposure >4.2% of time	Proximal: NP. Distal: 5 cm above LES
Sereg-Bahar (2015)[17]	Positive DeMeester score	NP
Falk (2015)[110]	Proximal acid episode >1% of 24 h	Proximal: below UES. Distal: 5 cm above LES
Na (2016)[111]	Proximal episode ≥1 time/24 h	Proximal: above UES. Distal: esophagus. Proximal: hypopharynx
Cumpston (2016)[112]	≥1 proximal events or >40 proximal extent impedance events	Distal: 5-10 cm above LES
Hoppo (2012)[53]	≥1 events daily and/or full column reflux; reflux 2 cm distal to the UES >4/d (24 h)	Proximal probe: 0.5 cm above UES. Distal probe: esophagus 5 cm above LES
Nennstiel (2016)[98]	Distal probe: pH≤4 (4.0% time). Impedance: >73 fluids/22 h or esophageal mixed reflux episodes	Proximal probe: NP. Distal probe: esophagus 5 cm above LES.
Jung (2017)[113]	Proximal episode >1 time/24 h. Acid/nonacid: every event: pH <4 / pH >4. Mixed: pH >4 and pH <4	Proximal probe: hypopharynx. Distal probe: low esophagus
Formánek (2017)[114]	Proximal probe ≥6 events daily	Proximal probe: 2 cm above UES. Distal probe: low esophagus
Weitzendorfer (2017)[115]	Number of reflux episode >73 or DeMeester exceeded 14.7	Proximal probe: 5 cm above LES. Distal probe: 15 cm below the LES.
Kim (2017)[116]	Proximal episode ≥1 time/24 h	Proximal probe: 25 cm above LES. Distal probe: 6 cm above LES
Du (2017)[117]	Total acid exposure time pH <4 >1% of time	NP
Dulery (2017)[118]	≥1 proximal events preceded by retrograde impedance drop esophageal distally and proximally and without swallow event.	Proximal probe: 0.5 cm above UES. Distal probe: low esophagus
Wang (2017)[119]	Proximal probe: decrease in pH by >2 units within 30 s to a value <4 units	Proximal probe: 0.5-1 cm above UES. Distal probe: 5 cm above LES
Tseng (2018)[120]	Distal probe: pH ≤4 (4% time)	Proximal probe: NP. Distal probe: esophagus 3 cm above LES
Lee (2018)[90]	Proximal episode >1 time/24 h. Acid/nonacid: every event: pH <4 / pH >4. Mixed: pH >4 and pH <4	Proximal probe: hypopharynx. Distal probe: low esophagus
Suzuki (2018)[121]	≥1 events daily and/or full column reflux, reflux 2 cm distal to the UES >4/d (24 h).	Proximal probe: 0.5 cm above UES. Distal probe: esophagus 5 cm above LES
Lee (2018)[18]	Acid reflux episodes: decrease in pH <4 for at least 5 s	Proximal probe: 25 cm above LES. Distal probe: 6 cm above LES

Abbreviations: LES, lower esophageal sphincter; LPR, laryngopharyngeal reflux; NP, not provided; UES, upper esophageal sphincter.
[a]In this table, we considered studies of patients primarily diagnosed with LPR; research focusing on patients with resistant LPR was not considered.

recent meta-analysis of 11 studies suggested that sensitivity and specificity of salivary pepsin detection would be 64% and 68%, respectively,[142] but in practice, the lack of a gold standard limits us in the determination of the epidemiologic characteristics of this approach. In fact, there was notable heterogeneity in the diagnosis method, the exclusion criteria, and the material used for the pepsin detection in these 11 studies.[142,143] This point is crucial because the reliability of the pepsin detection seems to depend on the technique (immunoassay, ELISA, or Western blot), the threshold for determining a test result to be positive or negative, the number of positive samples needed to assign a LPR diagnosis, and the timing of samples themselves.[143] In the current literature, these characteristics substantially vary among studies, and there is no consensus about the best time for the sample collection. Recently, Na et al suggested that the best time for the pepsin collection would be in the morning upon waking,[111] but future studies are needed to confirm these data with a large number of patients because LPR usually occurs while upright and during the daytime.[4] Another important point that is underestimated in the current literature is the potential impact of trypsin and biliary salts on the mucosal damage, although recent data supported the key role of these molecules.[17,90] Future research has to respond to many unanswered questions about the number and optimal timing for the sampling, the location and nature, the threshold values for pepsin testing, the impact of diet, and the reliability of detection of pepsin and biliary salts in the same sample.

In summary, there is no gold standard for the LPR diagnosis. However, it is accepted that patients with LPR symptoms, signs, and $\geq$1 proximal esophageal reflux episodes at the MII-pH can be considered patients with LPR. The use of MII-pH makes sense in comparison with oropharyngeal pH monitoring in regard to the detection of LPR and GERD that may coexist. In case of doubt or in case of symptoms, signs, but negative MII-pH, pepsin detection could be useful for the diagnosis. Future technologies are needed to improve the LPR diagnosis. We could imagine a 96-hour MII-pH with additional probes able to collect pepsin and other gastroduodenal enzymes in the pharyngeal tissue and measure their concentrations.

Treatment

Management for presumed LPR can include behavioral modifications and pharmacologic treatment. The use of physician counseling for diet and lifestyle modification of factors known to affect LPR remains very low.[144] However, recent studies suggested that diet and lifestyle modifications are an important part of treatment. Zalvan et al showed that patients with LPR who were treated with alkaline water and a Mediterranean-style diet had improvement similar to those placed on PPIs.[34] Similarly, our team found that patients with LPR who focused on dietary modifications in addition to PPIs did better with respect to LPR symptoms and vocal improvement than those who used PPIs alone (**Table 6**).[145] The potentiating effect of diet on the efficacy of PPIs was supported in a recent meta-analysis.[3] The positive effect of an alkaline and low-fat diet was even demonstrated to be helpful for patients whose symptoms were refractory to PPIs.[146]

Regarding pharmacologic treatment, PPIs have been the most prescribed drugs for reflux.[5,144] However, the superiority of PPIs over placebo remains poorly demonstrated.[3] Unfortunately, this uncertain benefit exists in a climate in which the costs of reflux treatment[7] and the side effects from PPIs are becoming increasingly recognized.[147] Naturally, these studies showing rough equivalency between PPIs and placebo are not meant to suggest that patients with true LPR will not benefit from PPI therapy; the inability of studies to demonstrate the role of PPIs in treatment likely reflects an inability to include only patients with reflux. Indeed, there is notable heterogeneity among studies according to diagnosis, inclusion and exclusion criteria, variability of treatment algorithms, and differences in measured outcomes. Our recent meta-analysis, which included 10 placebo randomized controlled trials comparing PPIs with placebo, identified 7 different methods for diagnosis, 10 different lists of exclusion criteria, 9 different therapeutic regimens, 10 different combinations of clinical outcomes used to assess response to treatment, and 3 different treatment durations.[3]

In light of increasing studies that identify acid and nonacid reflux as important LPR etiologies,[17,90,91] our therapeutic approach could evolve. The exclusive use of PPIs in the LPR therapeutic course can be challenged, since they are less effective on nonacid or mixed reflux.[27] Given the required alkaline pH for trypsin activity,[17] the administration of high doses of PPIs may be associated with a worsening of complaints.[17] It is possible that many patients who were considered resistant to PPI treatment in the previous studies (which used classical pH metry) just had mixed or biliary LPR. Alginate drugs make particular sense in the case of nonacid or mixed reflux or for patients with postprandial symptoms and, according to a recent article, could have similar efficiency to that of PPIs and alginate.[148,149] Moreover, in practice, the combination of magaldrate and alginate at bedtime may be useful for many patients with nonacid or mixed reflux according to MII-pH. H_2-receptor antagonists are second-line treatment regarding the short duration of action (4-8 hours) of these drugs.[150] In case of acid reflux, the prescription of twice-daily PPIs could be associated with better symptom improvement than a once-daily PPI prescription.[151]

Regarding patients who are resistant, the first step is to assess the treatment compliance, since 62.7% of such patients do not adequately take the treatment.[152] The second step consists of the exclusion of differential diagnoses that can be associated with similar symptoms and findings (**Table 7**). Patients who are truly LPR resistant, who have no cofactors, and who respect the treatment may benefit from additional gastrointestinal examinations (eg, manometry, gastrointestinal endoscopy) to identify some conditions explaining the therapeutic resistance (eg, hiatal hernia,

Table 6. Alkaline, Protein, and Low-Fat Diet.[a]

Lifestyle Habits	Foods to Favor	Foods to Avoid
1. Stress control	1. Meat, fish, chicken, eggs	1. Meat, fish, chicken, eggs
2. Tobacco and other addiction(s) reduction	Shrimps, lobster, shellfish, fresh and thin fish	Fat fish, fish oil (sardines, cods, herrings)
3. Reduction of size of meals	Chicken fillet (without skin)	Fat chicken
4. Hot lunch in place of hot diner	Turkey or duck (without skin and fat)	High-fat meat
5. Eat slowly	Low-fat meat (remove fat from meat)	*Kidneys, bacon, ground meat*
6. Do not talk while eating	*Veal cutlet, horse, pork tenderloin*	*Lamb chops, shoulder or legs of lamb*
7. Avoid tight clothing	*Rindless, fatless, cooked ham*	*Ribs, rib steak, foie gras, delis, sausage*
8. If possible avoid the following drugs:	*Steak, fillet, striploin roast veal, veal, chop*	*Pork chops, roast, and shoulder, salami*
Nonsteroidal anti-inflammatory drugs	Egg white	*Paté, tripes*
Corticosteroids, aspirin, theophylline	Other:……..	Other:……..
Progesterone, iron supplementation	2. Dairy products	2. Dairy products
Calcium channel blockers	Low-fat cheese	Chocolate, ice cream, whole milk
Nitroderivatives, anticholinergic	Skim milk	Hard cheese, full-fat cheese
If heartburn	Other:……..	*Goat cheese, cheddar, Roquefort, Fontina, gruyere, parmesan, munster, etc*
1. Reduction of overweight		
2. Elevating the head of the bed		Other:……..
	3. Cereals and starches	3. Cereals and starches
Laryngopharyngeal reflux treatment	Oat, wheat, cracker, pasta, boiled potatoes	Nut, cashew, hazelnut, peanut
Drug: ……	Wholemeal or brown bread, rice, brown rice	French fries and frying, chocolate cookies
To take: before - during - after	Other:……..	White bread
		Other:……..
Meals (circle the adequate response):	4. Fruit and vegetables	4. Fruit and vegetables
Breakfast	Agave, asparagus, cooked mushrooms	Shallot, spicy, chili
Lunch	Banana, melon, peach, ginger, spirulina	Onion, garlic, tomato (sauce/raw tomato)
Diner	Broccoli, celery, cauliflower, fennel, tofu	Aspartame
Laryngopharyngeal reflux treatment	Green beans, lentil, chickpeas, turnip, parsley	Rhubarb, blueberry, beet/cane sugar
Drug: ……	Other:……..	Other:……..
To take: before - during - after	Preparation:	
	Cooked by steaming or boiling in water	
Meals (circle the adequate response):	5. Beverage	5. Beverage
Breakfast	Chamomile	Strong alcohol, red and rosé wines
Lunch	Water, alkaline water	Sparkling beverage (water, soda, beer, etc)
Diner	Appel/pear juices (no sugar added)	Coffee, tea
Laryngopharyngeal reflux treatment	Melon/banana juices (no sugar added)	Citrus juices (orange, lemon, grapefruit)
Drug: ……	Other:……..	Other:……..
To take: before - during - after	6. Greasy substances	6. Greasy substances
	Olive oil	Butter, spicy oils
Meals (circle the adequate response):	Other:……..	Sauces (mayonnaise, mustard, ketchup, etc)
Breakfast		Other:……..
Lunch	7. Sugar	7. Sugar
Diner	Honey	Sweets

[a]Protein foods improve the esophageal sphincters tonicity. Carbonated beverages, caffeine, alcohol, fat, and tobacco decrease the sphincter tonicity promoting laryngopharyngeal reflux.[145] Acidic foods (spicy, caffeine, beer, chocolate, etc) promote the pepsin activity in refluxate gaz.

gastroparesis). For these patients, the inhibition of transient lower esophageal sphincter relaxations or, in preselected resistant cases (eg, severe hiatal hernia), fundoplication can be proposed.

Irrespective to the treatment scheme, it is recommended to treat patients for a minimum of 8 weeks, corresponding to the time necessary for the mucosal healing and regeneration. Ideally, an initial period of 3 months may be proposed, after which a therapeutic revision can be made for 3 additional months. Approximately 25% to 50% of patients would have a chronic course of the disease.[4] For this reason, patients could keep their diet and lifestyle changes. Physicians have to fully avoid the chronic prescription of PPIs in regard to their long-term side effects.[147]

Table 7. Differential Diagnoses of Laryngopharyngeal Reflux.[a]

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 (alcohol, tobacco pharyngolaryngitis)
Esophageal candidosis	Tuberculosis	Stress
Heterotopic esophageal gastric mucosa	***Rheumatologic/autoimmune disorders***	Anxiety
Neoplasia	Rheumatic arthritis	Depression
Esophageal/sphincter motor disorders	Sjögren's syndrome	Drugs
Hypertonicity of upper esophageal sphincter	Laryngeal sarcoidosis	Anticholinergic (salivary hypofunction)
Hypertonicity of lower esophageal sphincter	Amyloidosis	
Achalasia	Granulomatosis with polyangiitis	
Esophageal spasm	Fibromyalgia	
Absent peristaltism	Allergy	
Hypercontractile esophagus	***Laryngeal musculoskeletal disorders***	
Gastroparesis	Function laryngeal disorders	
Other	Muscle tension dysphonia	
Rumination	***Benign or malign tumors***	
Aerophagia	***Anatomic disorders***	
	Size and shape of the epiglottis	
	Tongue tonsil hypertrophy	
	Uvula hypertrophy	
	Retroverted epiglottis (touching the posterior pharyngeal wall)	
	Traumatic and other	
	Laryngeal fracture	
	Upper aerodigestive tract injury	
	Cervical osteophytes	
	Aging voice	
	Upper aerodigestive tract neoplasia	
	Thyroid disease (nodules, goiter, etc)	

[a]This table was constructed according to publications focusing on differential diagnoses of the main prevalent laryngopharyngeal reflux symptoms (globus, dysphonia, throat clearing, and cough).[154-158]

In summary, the high heterogeneity among randomized controlled trials comparing PPIs and placebo leads to inconclusive results about the superiority of PPIs over placebo. In fact, mild LPR could be treated with diet and behavioral changes, and in case of nonresponse, patients could benefit from a personalized therapeutic scheme according to the reflux profile at the MII-pH results. The association of diet with many drugs, including PPIs, alginate, and magaldrate, could significantly improve the therapeutic efficacy. In case of nonresponse to treatment, therapeutic compliance should be assessed.

Implications for Practice

Laryngopharyngeal symptoms are prevalent, but the exact prevalence of LPR is unknown. Future epidemiologic studies should focus on objective examination of patients with LPR symptoms and signs to better delineate LPR incidence and prevalence. Local lifestyle habits, diet, and the prevalence of cofactors associated with similar complaints should be taken into consideration.

The prevalence of LPR symptoms and signs strongly depends of the characteristics of studies—that is, the diagnostic method, inclusion/exclusion criteria, and clinical tools used. The assessment of signs and symptoms with complete tools is needed with consideration of the type of reflux (nonacid, acid, mixed). The methods used to assess signs are important and should be as objective as possible. The use of software to assess mucosal inflammation is another future way.

The recent findings about the role of pepsin and biliary salts and the development of MII-pH open new prospects within the scope of diagnosing and treating LPR. Future diagnostic direction could associate symptoms, signs, MII-pH, and pepsin and trypsin detection to obtain a multiparameter diagnostic approach as a gold standard. Clinical tools

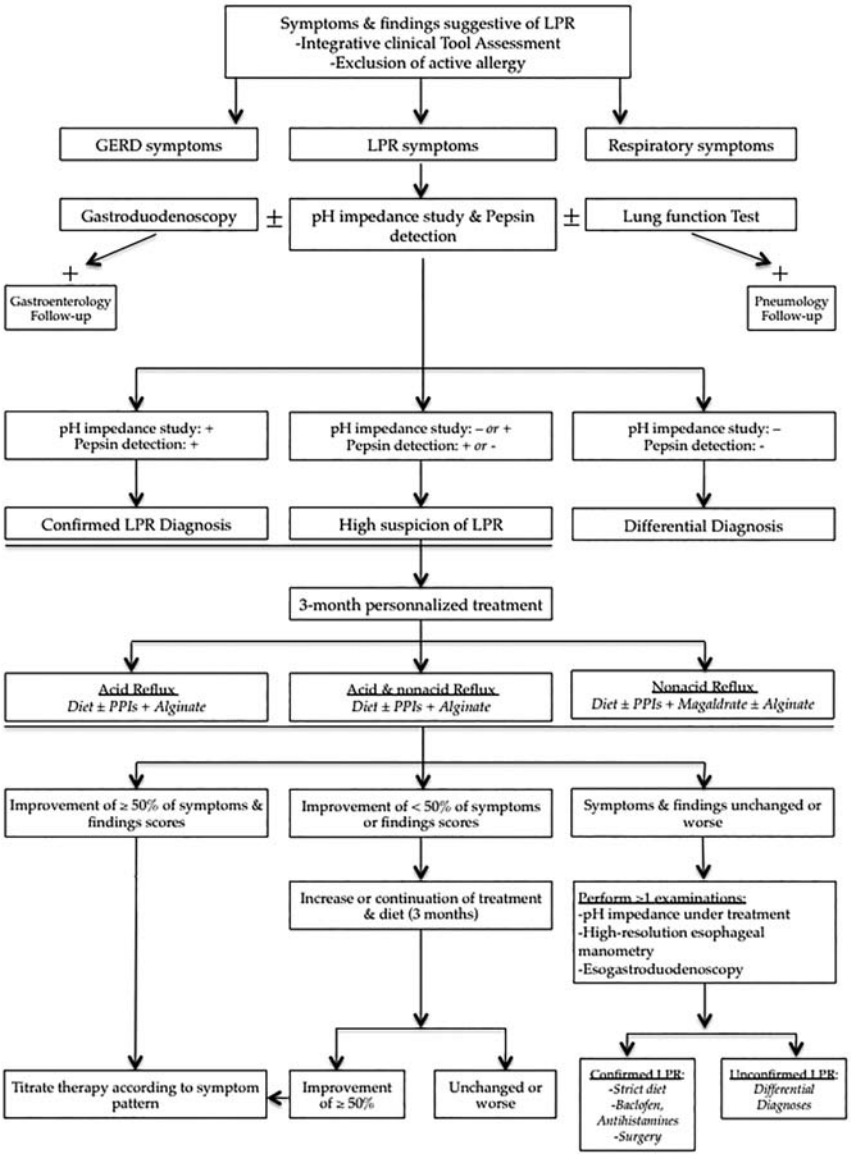

Figure 4. Algorithm for management of suspected or confirmed laryngopharyngeal reflux (LPR). In practice, the use of pepsin detection can be useful for patients with suspected LPR with negative impedance-pH monitoring. Treatment is based on diet ± proton pump inhibitor (PPIs) + alginate or magaldrate according to the LPR characteristic (acid, nonacid, or mixed reflux). The improvement of ≥50% of LPR signs and symptoms leads to a treatment titration.[148] Pending the development of new complete clinical tools (Reflux Symptom Score and Reflux Sign Assessment), the use of clinical tools involves the adoption of validated thresholds for the diagnosis (Reflux Symptom Index >13 and Reflux Finding Score >7).

should include a screening of GERD and pulmonary symptoms that are associated with LPR. The assessment of these patients in multidisciplinary settings (ie, involving clinicians from different specialties) is also crucial. The development of a future clinical model to estimate the pretest probability of abnormal pH among patients who failed PPI therapy could improve the diagnosis approach.[153]

According to the LPR profile and the clinical manifestation, a personalized treatment can be proposed. Diet and lifestyle changes should be considered as the first step of treatment and could be sufficient to treat mild LPR. The addition of alginate and magaldrate to PPIs should improve the therapeutic management of nonacid and mixed LPR.

With regard to the high level of controversy about prevalence, clinical manifestation, diagnosis and treatment, otolaryngologists, gastroenterologists, and surgeons have to define a multiparameter diagnostic approach with consensual MII-pH criteria and an overall therapeutic management plan for reflux. For this last point, we have proposed a new management algorithm that is currently a course of reflection for the future debates (**Figure 4**).

Author Contributions

Jerome R. Lechien, substantial contributions to the conception or design of the work; & the acquisition, analysis, or interpretation of data for the work; drafting the work; final approval of the version

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