The Dubai Definition and Diagnostic Criteria of Laryngopharyngeal Reflux: The IFOS Consensus

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Objective: The objective of this work was to gather an international consensus group to propose a global definition and diagnostic approach of laryngopharyngeal reflux (LPR) to guide primary care and specialist physicians in the management of LPR.

Methods: Forty-eight international experts (otolaryngologists, gastroenterologists, surgeons, and physiologists) were included in a modified Delphi process to revise 48 statements about definition, clinical presentation, and diagnostic approaches to LPR. Three voting rounds determined a consensus statement to be acceptable when 80% of experts agreed with a rating of at least 8/10. Votes were anonymous and the analyses of voting rounds were performed by an independent statistician.

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Results: After the third round, 79.2% of statements ($N = 38/48$) were approved. LPR was defined as a disease of the upper aerodigestive tract resulting from the direct and/or indirect effects of gastroduodenal content reflux, inducing morphological and/or neurological changes in the upper aerodigestive tract. LPR is associated with recognized non-specific laryngeal and extra-laryngeal symptoms and signs that can be evaluated with validated patient-reported outcome questionnaires and clinical instruments. The hypopharyngeal–esophageal multichannel intraluminal impedance–pH testing can suggest the diagnosis of LPR when there is >1 acid, weakly acid or nonacid hypopharyngeal reflux event in 24 h.

Conclusion: A global consensus definition for LPR is presented to improve detection and diagnosis of the disease for otolaryngologists, pulmonologists, gastroenterologists, surgeons, and primary care practitioners. The approved statements are offered to improve collaborative research by adopting common and validated diagnostic approaches to LPR.

Key Words: consensus, definition, diagnostic, gastroesophageal, guidelines, laryngitis, laryngopharyngeal, reflux.

Level of Evidence: 5

INTRODUCTION

Laryngopharyngeal reflux (LPR) was initially defined as the backflow of stomach contents into the laryngopharynx.[1] LPR is a disease with different pathophysiological mechanisms and clinical picture than classic gastroesophageal reflux disease (GERD).[2–4] Various definitions and diagnostic approaches have been published but a universally accepted LPR definition remains lacking.[5,6] LPR symptoms and findings are prevalent in primary care, otolaryngological, and gastroenterological consultations.[2,7–10] The non-specificity of symptoms and findings attributed to LPR and the poor effectiveness of empiric proton pump inhibitor (PPI)-therapy make the diagnosis challenging, resulting in over- and under-diagnosis of the condition.[11–13] Finally, the role of additional testing such as impedance pH-monitoring, remains poorly defined.[14–17] In this current climate of uncertainty, an international group of experts from the five continents was convened to develop consensus statements regarding definition and diagnosis of LPR. The evidence used to create the statements of this modified Delphi consensus study was based on expert opinion and was not always based on other guidelines developed from systematic reviews or randomized trials. Because of this methodology, this work should not be considered a clinical guideline. Rather, the IFOS consensus is offered to disseminate expert knowledge from thought leaders who treat and study LPR, and is presented to aid primary care and specialist physicians in the diagnosis of LPR.

METHODS

Development of the consensus definition and diagnostic approach to LPR combined principles of evidence-based medicine and a modified Delphi approach.[18] Experts were invited to vote anonymously on a series of proposed statements through SurveyMonkey® (San Mateo, California, USA), allowing each

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participant to complete the survey only once. The statements were written and proposed by a Consensus Committee (CC) of 8 LPR-experienced board-certified physicians selected on their expertise in LPR. The results of the voting rounds were analyzed by a non-voting chair who performed the statistical analyses. The CC provided systematic or state-of-the-art literature reviews to the panel of experts to steer the consensus process away from clinical opinion and towards methodologically sound evidence.[19] The CC agreed to organize the Delphi process through a maximum of 4 voting rounds, each separated by discussion and revision of statements that did not reach validation on prior voting. In iterative fashion, statements that fell short of validation were either improved to the point of reaching consensus or were discarded, with the goal of the statements reaching consensus where possible. The establishment of present consensus was conducted through five steps:

1. The selection of the members of the CC and the expert panel.
2. The draft statement development by the CC.
3. The systematic literature review to support the proposed statements, which included the grading of the evidence.
4. Repeated voting rounds and panel discussion from the results of the second to the third voting round.
5. Writing the present paper and obtaining endorsement by the International Federation of Otorhinolaryngological Societies (IFOS).

Consensus Committee and Expert Panel

The CC was composed of eight experts who come from the five continents. These experts are all members of their respective regional premier scientific societies in otolaryngology-head and neck surgery. The CC selected the relevant papers in the literature review process and developed the initial statements, which were then submitted to the panel of experts. The panel of experts and the CC were organized by the first author and the two senior authors.

The voting panel assembled was comprised of 48 experts from 18 countries. The scientific backgrounds of the experts, including individual numbers of publications on LPR, and inclusion criteria of being chosen an expert are available in Appendix S1. Briefly, experts published a mean (SD) of 34.6 (41.0) peer-reviewed papers on reflux diseases according to PubMED. With the exception of the one voting panel expert chosen in an effort to be inclusive of the African continent, experts were required to have at least one publication specifically on LPR, but most experts, from the required five continents (North America, South America, Europe, Oceania, Asia, Africa), had more than one publication on LPR. The expert voting panel members were required to be currently active, clinically or through research (not retired), and the panel required at least 20% of experts to be outside the field of Otolaryngology but with an expertise in reflux. The CC developed an initial list of 48 statements, which covered a range of important topics related to diagnosis of LPR, including definition of LPR, pathophysiology and differences compared to GERD ($N = 6$); prevalence and incidence of LPR ($N = 4$); contributing factors and associations with other otolaryngological conditions ($N = 6$); symptoms ($N = 4$); findings ($N = 4$); and additional examinations ($N = 24$).

Literature Search

The PubMed, Cochrane Library, and Scopus database literature search were conducted by three authors (J.R.L., S.S., M.R.B.) for relevant peer-reviewed publications in English-language using relevant keywords (Reflux/pH metry/Impedance/Diagnosis/Definition/Symptoms/Signs) to identify and grade the available evidence that was included to support the development of statements. The literature search was performed according to the PRISMA Statements for systematic review. The following databases were used for the search: PubMED, Scopus and Cochrane Library from 1990 to 2022. Relevant publications were identified, and references of the included papers were further screened for additional research. Several search strings were used that are too numerous to list in the present paper. The complete list of the search strings may be obtained from the first author. The reviewers reviewed each of the abstracts and selected articles for further review. The full texts of selected papers were available to the expert panel for the Delphi process.

Voting Rounds and Discussion

The Delphi process lasted 24 months. Ultimately, there were three voting rounds, separated by periods of time for revision and discussion between voting rounds. In each voting round, a 10-point Likert scale was used to rate each proposed statement from 1 (strongly disagree) to 10 (strongly agree). Consensus acceptance was defined as a Likert rating of ≥8/10 by at least 80% of experts, thus statements reaching this goal were accepted. The analyses of the results of the voting round were performed by an independent statistician (K.H.). At the end of each round, the level of agreement was communicated to the panel as the percentage of experts who voted ≥8/10 for each proposed statement. Statements that returned with only 60%–80% of scores ≥8/10 were discussed by the CC and revised, based on feedback and comments provided by the voting panel—these revised statements were then subjected to additional voting. Statements that did not reach at least 60% agreement of ≥8/10 by the experts were discarded and were not subjected to additional revision or further voting. After the second voting round, a ZOOM® meeting (Zoom Video Communication Inc, San Jose, CA) was organized with committee members and the experts of the panel to further improve those statements that remained in the 60%–80% of scores ≥8/10 and which had not yet been either accepted or discarded.

Grades of Evidence

The assignments of the grade of evidence to the statements was performed by the CC with the GRADE system as is recommended for Position/Consensus papers.[20] The grade of the statement aimed to give a practical indication of the likely impact of further research on confidence in the estimate effect. Based on similar work conducted in gut disease,[19,21] the CC members assigned one of the following grades to each statement:

- High (A): future investigations are unlikely to change our confidence in the estimate effect.
- Moderate (B): future investigations are likely to have an important impact on our confidence in the estimate effect and may change the estimate effect.
- Low (C): future investigations are likely to have an important impact on our confidence in the estimate effect and are very likely to change the estimate effect.
- Very low (D): any estimate of effect is uncertain.

The final assessment of grade was performed by the CC through a consensus discussion.

Endorsement by the International Federation of Otolaryngology Societies

The results of the Delphi process and the present publication were endorsed by the YO-IFOS and the IFOS as the "first world consensus for the definition and the diagnosis of laryngopharyngeal reflux." Because the first IFOS congress to be held after the voting rounds was complete was held in Dubai (January 2023) and the results first presented there, the name
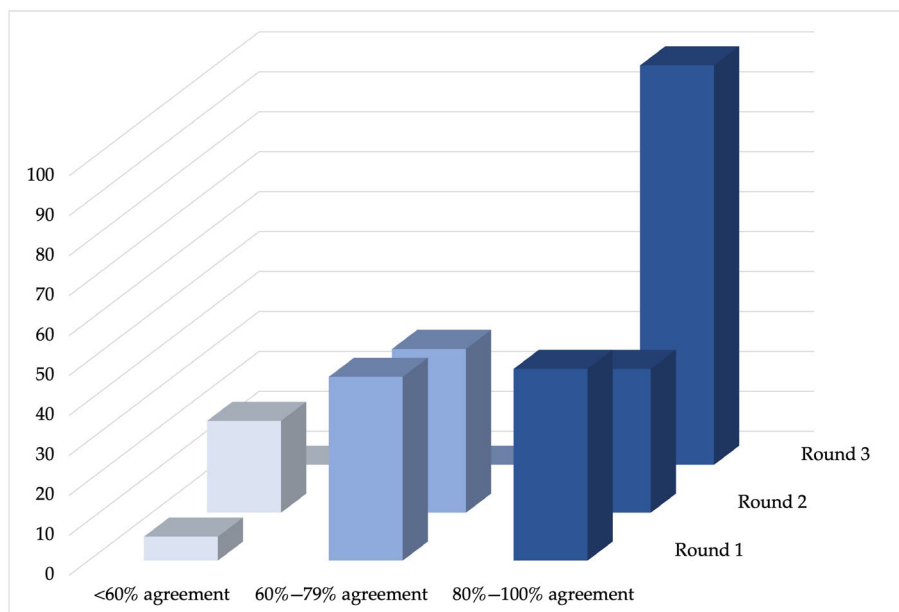
Fig. 1. Percentage of unvalidated and validated statements throughout the three voting rounds. From the second round to the third round, four items were merged into two items. Thus, seven statements were submitted to the third voting round in place of nine items. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

for this LPR consensus is the Dubai Definition and Diagnostic Criteria of LPR.

RESULTS AND DISCUSSION

Of the 48 statements initially presented, 38 statements (79.2%) reached agreement considering definition, pathophysiology, and differences with GERD (N = 3); prevalence/incidence of LPR (N = 1); contributing factors (N = 2) and associations with other otolaryngological conditions (N = 3); symptoms (N = 4); findings (N = 4); and additional examinations (N = 21). Among them, 23 statements reached consensus after the first round of voting, with 8 and 7 additional statements subsequently reaching consensus after the second and third voting rounds, respectively. The level of consensus increased through the successive voting rounds, with a higher level of consensus in the third round (Fig. 1). All statements proposed in the third round reached consensus. The final validated statements and the related grades of evidence are available in Table I. Several papers dedicated to definition, clinical picture, associations, and diagnostic approaches were reviewed and considered for the discussion of statements (Appendix S2). Figure 2 summarizes LPR-recognized symptoms, findings, and indications of additional examinations as put forth in agreement by our panel of experts. An executive summary of key position statements is reported in Table II.

Definition, Pathophysiology, and Differences with GERD (Statements 1–5)

The alternative names are related to the clinical characteristics of LPR. Because GERD-symptoms and endoscopic findings are absent in many patients,[22,23] some authors use the terms "silent," "atypical," "pharyngeal,"

"proximal," or "full column," reflux.[24] They highlight the findings specifically identified on objective reflux monitoring such as HEMII-pH.[24] The terms "extraesophageal reflux," "reflux laryngitis," and "pharyngolaryngeal reflux" may be assigned based on either features on reflux monitoring or the clinical observation of symptoms and signs caused by reflux that has reached the larynx/pharynx.[24]

From a pathophysiological standpoint, pepsin is involved in the development of inflammatory reaction of the laryngopharyngeal mucosa and related LPR-symptoms and findings.[25] The pathophysiological mechanisms of pepsin and its cell toxicity were demonstrated in laboratory studies,[25,26] and the morphological changes of tissues were observed in vocal folds, laryngeal, and pharyngeal cells.[27] Bile salts were found in higher concentration in the saliva of LPR patients compared to controls[28] and may be associated with tissue changes at the microscopic level.[29] The neurological impact of LPR may manifest as laryngeal sensitivity[30] and as abnormalities of the upper esophageal sphincter (UES).[24]

The pathophysiology of GERD has been extensively studied and primarily involves transient and inappropriate lower esophageal sphincter (LES) relaxation or LES hypotonia with the backflow of gastric content into the esophagus and subsequent troublesome symptoms and/or complications.[19] LPR has the additional process of retrograde flow above the UES into the laryngopharynx.[15] In that way, GERD and LPR share some common pathophysiological mechanisms, although with notable differences in physiology (UES relaxation and deposit of gastric content into the pharynx) and clinical picture (absence of heartburn and GERD-related esophageal symptoms in some patients). The presence of GERD should be a factor when considering the likelihood of LPR.[31,32] Indeed, Groome et al. demonstrated in a cohort of 1383 GERD patients that there is a

TABLE I.
Definition, Epidemiological, and Association Statements (1 to 3), Clinical Statements (4 to 5) and Diagnostic Statements (6).

N	Statements	% (R)	Grade
1. Definition, pathophysiology and differences with GERD			
1.	LPR has many alternative names including but not limited to silent reflux, pharyngolaryngeal reflux, extraesophageal reflux, atypical GERD, reflux laryngitis, full column reflux, pharyngeal reflux, and proximal reflux.	90 (1)	NA
2.	LPR is a disease of the upper aerodigestive tract resulting from the direct and/or indirect effects of gastroduodenal content reflux, inducing morphological and/or neurological changes in the upper aerodigestive tract.	93 (1)	A
3.	LPR and GERD share some common pathophysiological mechanisms but may present with different clinical pictures.	91 (2)	A
4.	The following may be factors that impair gastroesophageal function and be associated with the development of LPR: tobacco use; obesity; primary esophageal dysmotility; diets high in fat, salt, sugar, mint or acidic content; diets low in protein.	92 (3)	B
5.	The consumption of alcohol may be a factor that may impair gastroesophageal function and may be associated with the development of LPR.	83 (1)	B
2. Prevalence and incidence			
6.	The prevalence and incidence of LPR are unknown because no objective gold standard parameters are agreed upon for confirming diagnosis.	83 (1)	C
3. Associations between LPR and otolaryngologic diseases			
7.	Although future studies are needed to confirm this association, LPR may be associated with vocal process granuloma.	83 (1)	B
8.	LPR may impact the clinical course and therapeutic response of patients with asthma, but future prospective studies are needed to confirm the mechanisms underlying the association.	80 (2)	C
9.	The relationship between LPR and the following ear, nose and throat diseases requires clarification through future studies: paradoxical vocal fold movement; laryngotracheal stenosis; spasmodic dysphonia; laryngeal infections; obstructive sleep apnea; recurrent respiratory papillomatosis; chronic nasal obstruction; olfactory dysfunction; laryngeal cancer; pharyngeal cancer; oral cancer.	90 (3)	C
4. Symptoms of LPR			
10.	LPR may be associated with the following nonspecific ear, nose, and throat symptoms: dysphonia, dysphagia, throat pain, globus sensation, throat clearing, postnasal drip or throat sticky mucus, troublesome cough, cough after lying down/eating, heartburn, and regurgitations.	90 (2)	B
11.	Typical esophageal symptoms of GERD such as heartburn and digestive symptoms may be present in some LPR patients.	91 (2)	A
12.	The association between LPR and the following symptoms requires future study: odynophagia, ear pain, burning tongue, halitosis, dyspnea, chest pain, nausea, acid brash, belching, and dyspepsia.	93 (3)	B
13.	Given the diverse and non-specific nature of symptoms, validated patient-reported outcome questionnaires would ideally be employed in systematic fashion for the diagnosis and follow-up of LPR.	81 (1)	A
5. Findings of LPR			
14.	No specific laryngeal signs are diagnostic of LPR. However, commonly observed signs associated with LPR symptoms may include arytenoid erythema, posterior commissure hypertrophy and erythema, interarytenoid granulation, diffuse laryngeal erythema, vocal fold edema/erythema, pharyngeal erythema, ventricular band erythema/edema, subglottic edema/erythema, post-cricoid erythema/edema, endolaryngeal mucus, and pharyngeal sticky mucus.	89 (3)	B
15.	Vocal process granuloma can be a sign of LPR, and their presence should prompt LPR evaluation or treatment in the setting of suggestive clinical symptoms.	80 (1)	B
16.	Regarding the non-specific nature of examination findings, use of a validated instrument would be ideal when assessing LPR-associated findings for both the diagnosis and the follow-up of LPR.	81 (1)	A
17.	LPR-related laryngeal findings have weak correlations with reported symptoms, esophageal findings on endoscopy, and results of reflux-monitoring studies. Therefore, diagnosis of LPR should not be made based on laryngeal findings alone.	80 (1)	A
6. Additional examinations			
6.1. Upper gastrointestinal endoscopy or transnasal esophagoscopy			
18.	The findings of upper gastrointestinal (GI) endoscopy or transnasal esophagoscopy (TNE) may be normal in LPR patients.	91 (1)	A
19.	Upper GI endoscopy should be performed for all patients with LPR-related symptoms who do not respond to empirical therapeutic trial to evaluate the presence of esophagitis, hiatal hernia, inlet patch of gastric mucosa in the esophagus, gastritis, Helicobacter pylori infection and if HEMII-pH testing demonstrates reflux that was unresponsive to empiric medication trials.	81 (1)	B
20.	Upper GI endoscopy should be performed for all patients with LPR-related symptoms and concomitant "alarm" features, such as severe dysphagia, hematemesis, unexplained weight loss, or a family history of upper GI tract cancer.	96 (1)	A
6.2. Esophageal manometry			
21.	High-resolution manometry is indicated to evaluate for esophageal dysmotility and/or to assist in the placement of reflux monitoring probe in patients who do not respond to an empiric treatment for suspected LPR.	81 (1)	C
6.3. Impedance/pH-monitoring			
22.	Single-channel (esophageal) or dual-channel (esophageal-esophageal) pH probes are useful for diagnosing GERD but not adequate for diagnosing LPR because of lack pharyngeal sensor and lack of consideration of non-acid event.	85 (3)	A
23.	If HEMII-pH is unavailable, an empirical treatment covering acid, weakly acid and nonacid LPR may be prescribed and evaluated at 3 months. Treatment success of LPR should be based on improvement of the patient's LPR-symptoms.	81 (3)	B
24.	The HEMII-pH results may provide guidance as to appropriate nature, dosing, and timing of medications for the specific patient according to the type of LPR (acid, weakly acid, and nonacid) and time of occurrence (upright and daytime and/or nighttime)	85 (3)	B

(Continues)

TABLE I.
Continued

N	Statements	% (R)	Grade
25.	Triple-channel (dual esophageal and pharyngeal) pH-only studies may detect acid pharyngeal reflux events but they are not sufficient to rule out LPR disease as they may miss weakly acidic and nonacidic pharyngeal events.	83 (1)	A
26.	HEMII-pH monitoring has to respect the following placement characteristics:	83 (1)	B
	1. Proximal pH sensor in the hypopharyngeal cavity at 0.5 cm to 1 cm above upper esophageal sphincter; or within the sphincter.		
	2. Distal pH sensor in the esophagus as close to 5 cm above lower esophageal sphincter as possible.		
	3. At least 2 impedance sensor pairs in the esophagus.		
	4. At least 1 impedance sensor pair in the pharyngeal cavity. It is recommended to control the placement of the upper pH sensor by flexible laryngoscopic or manometric guidance. The recommended duration of the examination is 24-h. During the 24-h testing, the patient should continue their normal diet and activities.		
27.	On HEMII-pH, hypopharyngeal acid event consists of an event with a pH <4.0. A hypopharyngeal weakly acid reflux event consists of an event with a pH between 4.0 and 7.0. A hypopharyngeal alkaline reflux event consists of an event with pH > 7.0.	87 (1)	A
28.	The analysis of the 24-h recording must respect the following:	81 (1)	B
	1. Exclusion of reflux events during meals.		
	2. Pharyngeal reflux event diagnosed only when a reflux event originating from the distal most impedance channel reaches the pharyngeal channels in a retrograde fashion.		
	3. Manual analysis to identify reflux events that the computer may have reported incorrectly.		
29.	The severity of LPR seen on HEMII-pH or oropharyngeal pH monitoring is not necessarily correlated with the severity of symptoms and findings.	80 (1)	A
30.	While HEMII-pH is promising as an objective tool for diagnosing LPR, the correlation between its findings and treatment outcomes remains limited. Controlled studies are needed to validate the value of this technology in predicting treatment outcomes.	91 (1)	A
31.	Reflux monitoring for LPR, whether using HEMII-pH, MII-pH, or pH-metry, should be performed off acid suppression medications, beginning at least 7 days prior to the study.	81 (1)	B
32.	The LPR diagnosis may not be confirmed with esophageal catheters that are configured with two esophageal pH sensors and without impedance or pH sensors in the pharynx because (1) the proximal esophageal reflux events may not reach the hypopharynx and (2) the presence of reflux events near the UES may be altered by swallowing saliva.	83 (2)	A
33.	Hypopharyngeal-esophageal multichannel intraluminal impedance pH monitoring (HEMII-pH) is an objective tool to identify esophago-pharyngeal reflux events (acid, weakly acidic, or nonacid) and can suggest the diagnosis of LPR when there is >1 hypopharyngeal reflux event in 24 hours.	90 (2)	B
6.4. Pepsin saliva detection			
34.	Pepsin saliva detection is a noninvasive approach that may demonstrate reflux in the pharynx but not confirm the patient's symptoms are due to LPR.	83 (1)	B
35.	Pepsin may not be detected in saliva of an LPR-suspect patient, although HEMII-pH may confirm LPR.	81 (1)	A
36.	The pepsin saliva concentration may be influenced by (1) the patient eating before the saliva sample is produced and (2) the time of day the sample is acquired.	87 (1)	B
37.	Pepsin saliva detection may prove to be a useful adjunctive diagnostic test and/or screening test for LPR but requires further understanding of how diet and sampling frequency influence results.	85 (2)	B
6.5. Oropharyngeal pH-testing			
38.	The criteria for establishing an LPR diagnosis as determined by HEMII-pH are not transferrable to an oropharyngeal-only pH study.	80 (2)	A

Abbreviations: GERD = gastroesophageal reflux disease; HEMII-pH = hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring; LPR = laryngopharyngeal reflux; N = number; NA = not available; % (R) = percentage of agreement (R = round 1 vs. 2 vs. 3).

correlation between the severity of GERD and the development of LPR.[32] This observation was supported in a recent study in which patients with both GERD and LPR demonstrated higher numbers of pharyngeal reflux events on HEMII-pH testing than those with LPR but without GERD.[31]

The influence of tobacco component on esophageal motility and sphincter functioning was supported in a few studies.[33] Obesity is a well-known predisposing factor for GERD, and overweight or obese patients with GERD may demonstrate LPR more often on HEMII-pH testing.[31] As the peristaltic function of the esophagus is an important defense mechanisms against proximal migration of refluxate, the presence of a primary esophageal dysmotility may be associated with the development of LPR in some patients.[8] The importance of diet in the development and management of reflux is supported in many studies.[34,35] High-fat foods are known to be associated with a higher risk of reflux due to their association with a slower gastric emptying time, a decrease of LES

pressure, and an increase in esophageal acid exposure.[33] The impact of mint on sphincter tonicity was supported in some GERD studies,[33] while high-protein foods may increase in LES tonicity.[33,34]

Regarding coffee, authors did not reach agreement due to conflicting evidence in the literature. Indeed, some studies suggested that coffee (caffeine) ingestion may lead to heartburn in GERD patients[36] and decrease the LES pressure,[37] while others did not find negative impact of coffee on esophageal function.[38] Similar discussion occurred about tea, highlighting the recent meta-analysis investigating the association between tea consumption and the development of GERD in which authors reported that due to the existence of several subgroups of tea drinkers, some develop reflux disease while others do not.[39]

Prevalence and Incidence of LPR (Statement 6)
Because consensus definition and diagnostic method of LPR did not exist prior to the current attempt,

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                          ┌─────────────────────────┐
                          │  Suspicion of diagnosis │
                          └────────────┬────────────┘
              ┌──────────────────────────────────────────────┐
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Considered symptoms:
Dysphonia · Dysphagia
Throat pain · Throat mucus
Globus sensation · Throat clearing
Cough · Postnasal drip
Cough after lying down/eating
Heartburn and regurgitations.

Considered signs:
Arytenoid erythema · Interarytenoid granulation
Diffuse laryngeal erythema · Subglottic edema/erythema
Vocal fold edema/erythema · Endolaryngeal mucus
Pharyngeal erythema · Pharyngeal sticky mucus
Ventricle erythema/edema · Postcricoid erythema/edema
Posterior commissure hypertrophy/erythema Granuloma

Validated patient-reported outcomes questionnaires

Clinical validated instruments

Potential favoring factors:
Tobacco · Obesity
Primary esophageal dysmotility
High-fat, low-protein, salt, sugar, mint or acidic foods and beverages
Alcohol consumption

HEMII-pH

Unavailable

Available

3-month empirical treatment covering acid and nonacid reflux events

Diagnosis confirmation:
>1 pharyngeal reflux event/24-h

Manometry if:
-No response to treatment

GI/TN endoscopy if:
-No response to treatment
-Severe dysphagia
-Hematemesis
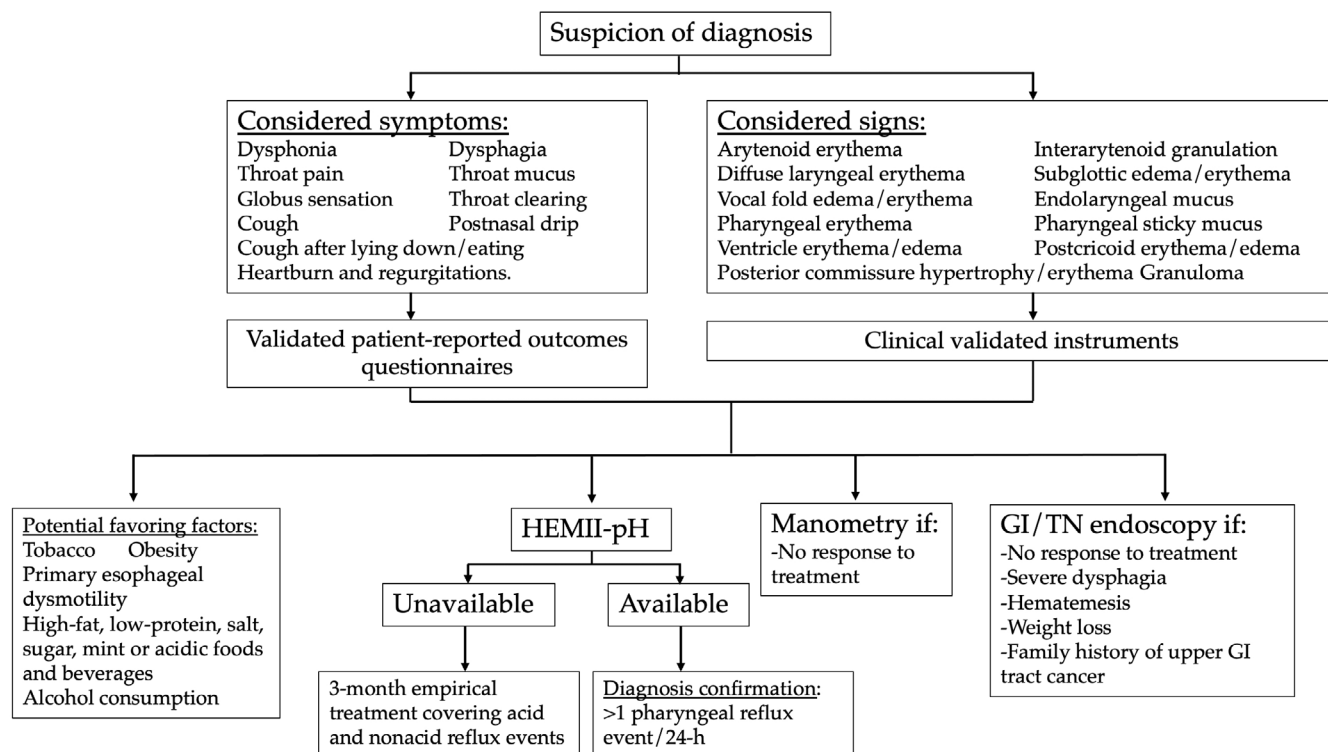-Weight loss
-Family history of upper GI tract cancer

Fig. 2. Symptoms, signs and additional examinations of laryngopharyngeal reflux (LPR). GI/TN = gastrointestinal/transnasal; HEMII-pH = hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring.

TABLE II.
Executive Summary of Key Position Statements.

Executive summary of key position statements

GRADE A: High-evidence findings

LPR results from direct and indirect effects of gastroduodenal content reflux, which induce morphological or neurological changes in mucosa.

LPR and GERD share some common pathophysiological mechanisms but may present with different clinical pictures. Heartburn and other typical digestive symptoms may be absent.

The LPR

Future diagnostic technologies, such as pepsin test or oropharyngeal pH-testing, are not yet evidence-based and require future studies to establish their reliability and potential cutoff for suggesting the diagnostic. The criteria established for HEMII-pH are not transferrable to oropharyngeal pH-testing.

Upper GI endoscopy may be normal in LPR patients and should be performed in patients with "alarm" features, such as severe dysphagia, hematemesis, unexplained weight loss, or family history of upper GI tract cancer.

GRADE B = Moderate-evidence Findings (state-of-the art, requiring future investigations)

The esophageal sphincter relaxations underlying pharyngeal reflux event may be due to tobacco, alcohol, obesity, primary esophageal dysmotility; diets high in fat, salt, sugar, mint or acidic content; and diets low in protein.

LPR is commonly associated with non-specific symptoms and laryngopharyngeal or oral findings for whom the use of clinical instruments is recommended to improve the baseline and posttreatment assessments and changes.

The LPR diagnosis can be based on symptoms or finding only but requires the identification of >1 acid (pH < 4.0), weakly acid (pH = 4.0–7.0) or non-acid (pH > 7.0) pharyngeal reflux event at the 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring.

The place and specific indications of esophageal manometry

GRADE C-D: Low-evidence findings requiring future investigations

The associations between LPR and the following conditions are plausible but not yet confirmed: Paradoxical vocal fold movement; Laryngotracheal stenosis; Spasmodic dysphonia; Laryngeal infections; Obstructive sleep apnea; Recurrent respiratory papillomatosis; Chronic nasal obstruction; Olfactory dysfunction; Laryngeal cancer; Pharyngeal cancer; Oral cancer, and Asthma.

Abbreviations: GERD = gastroesophageal reflux disease; GI = gastrointestinal; HEMII-pH = hypopharyngeal–esophageal multichannel intraluminal impedance–pH monitoring; LPR = laryngopharyngeal reflux.

estimates on the prevalence and incidence of LPR in the population vary widely. Prior studies have reported a 1%–30% prevalence of LPR-symptoms in otolaryngologic consultation,[40] or the general population,[7] but these symptoms are non-specific and may be encountered in many common otolaryngologic conditions.[40]

Associations between LPR and Otolaryngologic Diseases (Statements 7–9)

LPR has been implicated in the development of some ear, nose, and throat conditions based on the detection of pepsin in laryngeal, oral, sinonasal or middle ear mucosa or secretions,[25] for example, paradoxical vocal fold movement[41]; laryngotracheal stenosis[41,42]; spasmodic dysphonia[41]; obstructive sleep apnea[43]; recurrent respiratory papillomatosis[44]; chronic nasal obstruction[45]; olfactory dysfunction[46]; and laryngopharyngeal cancer.[47] In the same vein, several studies reported the occurrence of vocal process granuloma in patients with LPR based on pH-only testing results or clinical observations.[48]

The association between reflux, asthma severity, and therapeutic response has been extensively investigated over the past decades.[49,50] Despite methodological discrepancies in reflux diagnostic criteria across studies, LPR may be involved in the development of asthma, and antireflux therapy may improve asthma control when both conditions co-exist.[49,50] Because most pharyngeal reflux events are weakly acid,[51,52] HEMII-pH needs to be considered more regularly when considering the diagnosis of LPR in patients with asthma, and the other above-mentioned conditions.

SYMPTOMS AND FINDINGS (STATEMENTS 10–13)

LPR symptoms and findings are non-specific because they present as a mucosal inflammatory process in regions of the upper aerodigestive tract which may be commonly encountered in other prevalent otolaryngological conditions.[53,54] Patient-reported outcome questionnaires (PROM) assessing severity, frequency, and/or quality-of-life impact of symptoms are used to improve baseline and posttreatment evaluations.[40,55] The most common LPR PROM is the reflux symptom index (RSI),[56] which includes nine symptoms. As evidenced by the worldwide use of RSI, the association between LPR and these nine symptoms seems to have been ingrained into clinical practice. Accordingly, the expert panel of the current study also agreed on these symptoms. Throat pain, an additional symptom validated by the experts despite its absence in the RSI, has been associated with LPR in some clinical studies.[57,58] The development of the reflux symptom score (RSS),[59] and RSS-12,[60] with their subsequent validations in German,[61] Chinese[62] Korean,[63] Portuguese,[64] and Persian[65] include a broader list of symptoms potentially associated with LPR, for example, odynophagia, ear pain, dyspnea, or halitosis. However, the prevalence of these symptoms in the LPR population requires future controlled studies. This is especially true in regard to the association of LPR and dyspnea, specifically regarding the impact of LPR on asthma.[49,50] The term "respiratory reflux" may prove particularly appropriate.

To date, it is important to keep in mind that PROMs used in LPR (e.g., RSI, RSS) include non-specific symptoms, which may be found in other common laryngopharyngeal irritative conditions.[53,54] Thus, PROMs do not diagnose LPR but rather document laryngopharyngeal symptoms, both at baseline and as they change after treatment. PROMs cannot replace available objective diagnostic tools.

FINDINGS OF LPR (STATEMENTS 14–17)

Similar to symptoms, findings are non-specific and may be found in many inflammatory diseases of the upper aerodigestive tract mucosa.[66] The non-specificity of signs supports the interest in using clinical instruments to assess LPR.[67] In 2001, Belafsky et al., developed the reflux finding score (RFS), which considers most laryngeal signs.[68] The more recent development of the reflux sign assessment (RSA) has added oral and pharyngeal signs to the list of evaluation areas, for example, coated tongue, tongue tonsil hypertrophy or oropharyngeal erythema, that are felt to be more prevalent in LPR patients as compared to healthy individuals.[68] Laryngeal findings represent one more tool that may suggest possible LPR, but laryngoscopic signs alone cannot be considered diagnostic for LPR given their suboptimal specificity.

ADDITIONAL EXAMINATIONS

Upper Gastrointestinal Endoscopy or Transnasal Esophagoscopy (Statements 18–20)

The main complications of GERD, for example, esophagitis, esophageal hemorrhage, stricture, Barrett's esophagus and adenocarcinoma,[19] are less prevalent in LPR patients compared to GERD patients.[69] Erosive esophagitis was found in 10%–30% of LPR patients with an even lower proportion of patients (<10%) demonstrating Barrett's metaplasia.[69–71] These observations led to the discussion regarding the place of upper endoscopy in the workup of LPR patients, especially in those without GERD symptoms. The statements supported by our panel of experts may prove more cost-effective, taking into account patient complaints, medical and/or therapeutic history, and family history for consideration of upper endoscopy.

Esophageal Manometry (Statement 21)

Some anatomic and physiologic esophageal characteristics associated with LPR patients have been identified on high-resolution manometry. Notably, esophageal sphincters tonicity and length, intrabolus pressure, proximal or distal esophageal body contractility, intra-abdominal esophagus length and complete bolus clearance decreased among LPR patients.[8,72] Primary esophageal motility disorders per Chicago classification have also been identified in 43%–63% of patients with LPR symptoms, including ineffective esophageal motility (31%–41%), hypercontractile esophagus (4%–13%), and

disorders of esophagogastric junction outflow (8%–9%).[16] Some manometric features have also correlated with severity of symptoms and reflux, such as the proportion of failed swallows.[73,74] Thus, primary esophageal and sphincter dysfunction may contribute to both LPR severity and symptoms. However, these manometric findings are not specific to LPR, as they are also seen in GERD or other non-LPR conditions. The use of esophageal manometry is controversial in first-line management of LPR, and thus our experts only recommend high-resolution manometry specifically for the LPR population to identify a primary esophageal dysmotility disorder that may warrant treatment. It is not recommended as a primary diagnostic tool for LPR. Moreover, manometry may assist the placement of pH-impedance catheters.

Impedance/pH-monitoring (Statements 22–33)

The reflux monitoring technologies have evolved throughout the past 3 decades. Currently, most experts agree with the advantage of using HEMII-pH for detecting LPR, as recent studies found that LPR patients more frequently experience weakly acidic or nonacid pharyngeal reflux events.[41,75] Moreover, only a portion of proximal esophageal reflux events reach the pharynx,[76] while some patients may have a high proportion of gastroesophageal reflux events reaching the proximal esophagus or pharynx despite a low distal reflux burden,[5] therefore, making the traditional MII-pH less reliable than HEMII-pH in identifying LPR. In a recent systematic review of normative data for HEMII-pH, authors concluded that the 95th percentile thresholds were 10–73 events for proximal esophageal events, and 0–10 events for hypopharyngeal reflux events using HEMII-pH. The median number of pharyngeal reflux events among healthy individuals was 1,[5] which supported the cutoff proposed by the current experts. Future studies are needed to confirm this cutoff on large populations of healthy individuals as some papers report hypopharyngeal cutoffs in normal patients ranging from 1 to 4.[5] The expert panel agreed that any reflux monitoring should be performed off acid suppression therapy such as PPI, which needs to be discontinued at least 7 days prior to the test. Analysis of reflux monitoring studies for LPR should also follow the same basic principles of reflux testing for GERD, including the exclusion of reported mealtimes and the need for manual evaluation of the raw tracing data, rather than relying on automated computer analysis alone. Finally, the expert panel acknowledged the limited evidence currently in correlating reflux study findings and treatment outcomes. As proposed in statement 23, the unavailability of HEMII-pH may justify the use of an empiric therapeutic trial covering acid, weakly acid and non-acid LPR. However, this approach remains controversial: patients may experience unnecessary risk of adverse events through these empiric medication trials and increase costs are possible for both patients and the healthcare system.[40] Further prospective studies are needed to better clarify the prognostic value of objective reflux testing in predicting LPR symptom outcomes after anti-reflux therapy.

Pepsin Saliva Detection (Statements 34–37)

The sensitivity of pepsin saliva measurement ranges from 29.4% to 86.6% depending on the diagnostic pepsin concentration threshold, time of saliva collection, number of samples, and the method of measurements (e.g., ELISA, Western blot).[25,26,77] Moreover, studies reported inconsistencies in the associations between HEMII-pH, pepsin saliva measurements, and clinical findings, which may be attributed to the potential contribution of other gastroduodenal enzymes in mucosa inflammation and the development of symptoms and signs.[25] All of these issues limit the establishment of salivary pepsin as a conclusive test for LPR, and the expert panel agreed that its role remains as an adjunctive, but not primary, diagnostic test.

Oropharyngeal pH-testing (Statement 38)

A systematic review investigating normative ambulatory reflux monitoring evaluated oropharyngeal pH-testing findings in healthy individuals and reported that the 95th percentiles of oropharyngeal events at thresholds of pH < 4.0, pH < 5.0, and pH < 6.0 ranged from 0 to 2.5, 0 to 107.5, and 40 to 128, respectively.[5] The data may significantly vary from one study to another due to patient positioning and pH thresholds evaluated and some studies using simultaneous HEMII-pH and oropharyngeal pH-testing failed to demonstrate agreement in number of reflux events (oropharyngeal pH-testing missed true liquid events seen on HEMII-pH); in addition, the technological differences between HEMII-pH and lead to vastly different reported outcomes, thus the numbers obtained from oropharyngeal pH testing are very different and not transferable to HEMII-pH and MII-pH testings.[5] Oropharyngeal pH-testing remains controversial in its ability to truly diagnose LPR.[5]

CONCLUSION

A global consensus definition for LPR is offered to improve detection and diagnosis, for otolaryngologists, gastroenterologists, surgeons, and primary care practitioners. Such statements may allow collaborative research through studies adopting common language and validated diagnostic approaches.

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