European Archives of Oto-Rhino-Laryngology
https://doi.org/10.1007/s00405-024-09181-z

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European clinical practice guideline: managing and treating laryngopharyngeal reflux disease

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Received: 17 August 2024 / Accepted: 18 December 2024

Abstract

Objective To propose a European consensus for managing and treating laryngopharyngeal reflux disease (LPRD) to guide primary care and specialist physicians.

Methods Twenty-three European experts (otolaryngologists, gastroenterologists, surgeons) participated in a modified Delphi process to revise 38 statements about the definition, clinical management, and treatment of LPRD. Three voting rounds were conducted on a 5-point scale and a consensus was defined a priori as agreement by 80% of the experts.

Results After the third round, 36 statements composed the first European Consensus Report on the definition, diagnosis, and treatment of LPRD. The hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring is the gold standard for diagnosing LPRD (> 1 pharyngeal reflux event) and treating the LPRD with personalized therapy. The empirical treatment needs to be based on diet, stress reduction, and alginates or antiacids to address the acidic and alkaline reflux events. Proton pump inhibitors are kept for patients with acidic LPRD and gastroesophageal reflux disease (GERD) findings. The treatment needs to be as short as possible (minimum two months). The medication can be progressively reduced for patients with relief of symptoms. Changing medication class can be considered for refractory LPRD rather than an increase in drug doses.

Conclusion A consensus endorsed by the Confederation of European Otorhinolaryngology-Head and Neck Surgery Societies is presented to improve the management and treatment of LPRD. The approved statements could improve collaborative research through the adoption of common management approaches to LPRD.

Keywords Otolaryngology · Head neck surgery · Laryngopharyngeal · Gastroesophageal · Reflux · Consensus · Europe · European · Guidelines

Introduction

Laryngopharyngeal reflux disease (LPRD) is 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 [1]. LPRD is associated with non-specific symptoms and findings [2, 3], which are commonly found in common ear, nose, and throat conditions, i.e., chronic rhinosinusitis [4], allergy [5], or

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Published online: 24 December 2024

tobacco-induced laryngopharyngitis [6]. There are substantial differences between LPRD and gastroesophageal reflux disease (GERD) in terms of pathophysiology and the clinical picture [1, 7]. Given its high prevalence, GERD was extensively studied and both GERD diagnosis and treatment were standardized in successive international consensus and guidelines for many decades [8–10]. Despite a significant prevalence in Western countries [11], the number of studies dedicated to LPRD only significantly increased since the early 21st century [11], and the first international consensus dated from 2024 [1]. Thus, the Dubai consensus primarily focuses on the definition and diagnosis approach of LPRD [1]. The treatment of LPRD was not discussed due to important discrepancies between specialists, and the lack of evidence about the superiority of proton pump inhibitors (PPIs) over placebo [12]. Regarding the current climate of uncertainty in the management and treatment of LPRD, gastroenterologists, surgeons, and members of two scientific societies of the Confederation of European Otorhinolaryngology-Head and Neck Surgery (CEORLHNS) were convened to develop European consensus statements regarding the clinical management and treatment of LPRD.

Table 1 Characteristics of experts

Features	$N=23$
Gender	
Females	5 (21.7)
Males	18 (78.3)
Specialties (some having several specialties)	
General otolaryngology	12 (52.2)
Head & Neck Surgeon	4 (17.4)
Laryngology & Broncho-esophagology	16 (69.6)
Rhinology	2 (8.7)
Audiology and Phoniatrics	11 (47.8)
Otology	0 (0)
Visceral and Thoracic Surgeon	1 (4.3)
Digestive Surgeon	1 (4.3)
Gastroenterologist	1 (4.3)
Place of work	
Academic/University Hospital	20 (87.0)
Non-University Hospital	1 (4.3)
Private Practice	8 (34.8)
Clinical experience	
Year of practice (mean, SD)	19.3 ± 10.5
1–10 years	6 (26.1)
11–20 years	7 (30.4)
21–30 years	6 (26.1)
>31 years	4 (17.4)
Mean (SD) number of LPR patients/month	39.8 ± 28.5
Scientific experience	
Mean (SD) number of published paper/expert	31.2 ± 58.3

Abbreviations: N = number; SD = standard deviation

Materials and methods

Setting

The present consensus was based on principles of evidence-based medicine and a modified Delphi approach, adopting a similar approach for past gastroesophageal reflux disease guidelines (e.g., Montreal, Lyon Consensus) [13]. The statements were written and proposed by a committee of 3 board-certified otolaryngologist-head and neck surgeons (investigators) of the CEORLHNS and the young otolaryngologists of the international federation of otorhinolaryngological societies (YO-IFOS). The experts were invited to vote anonymously on statements through SurveyMonkey® (San Mateo, California, USA), allowing each participant to complete the survey only once. As per the previous consensus [1], the investigators provided meta-analysis, systematic or state-of-the-art literature reviews to the experts to steer the consensus process away from clinical opinion and toward methodologically sound evidence [8].

The Delphi process was organized through a maximum of 4 voting rounds. Non-validated statements were improved according to expert comments from one round to the next. Moreover, from the second to the third round, investigators proposed an online discussion for improving revisions of statements for the last rounds. The present consensus was conducted considering the following steps: (i) the selection of the experts on their expertise; (ii) the draft statement development by the investigators, (iii) the organization of the repeated voting rounds and panel discussion, and (iv) the GRADE evaluation of statements, (v) the writing of the present paper and v) the endorsement by the CEORLHNS societies (Union of the European Phoniatricians (UEP), European Laryngological Society (ELS), and YO-IFOS). The endorsement of UEP, ELS, and YO-IFOS aims to establish this work as European guidelines.

Investigator and expert panel

The investigators selected the relevant papers in the literature (the last recent systematic review or meta-analysis for the LPRD treatment) and developed the initial statements, which were then submitted to the panel of experts for review. The voting panel assembled was composed of 23 experts from 14 European countries. There were 19 otolaryngologists and head and neck surgeons, 2 gastroenterologists and 2 general surgeons. Otolaryngologists were members of their respective regional societies, including national societies, IFOS, or UEP.

The scientific backgrounds of the experts were summarized before inclusion and the following points were considered: individual numbers of publications on LPRD,

scientific presentations in congress and courses, and participation to previous consensus (Table 1). The experts were required to be currently clinically or through research active (not retired). Moreover, the following information was collected for experts: field of practice, number of years in practice since the end of the residency, place of practice, and the mean number of patients with suspected or confirmed LPRD seen every month.

Statement writing

The investigators developed an initial list of 38 statements, which covered the following LPRD topics: denomination and definition of LPRD ($N=2$), objective diagnosis testing ($N=7$), clinical diagnosis ($N=1$), and etiological ($N=8$), speech/voice-therapy ($N=2$), medical ($N=16$), or surgical ($N=2$) treatments. According to the importance of decreasing the medication intake for adverse events and cost burden for healthcare systems, the investigators developed 8 statements focused on known etiological factors of LPRD, including diet and autonomic nerve dysfunction, which was not available in previous reflux guidelines or consensus.

Voting rounds and discussion

The Delphi process started in August 2023 and lasted 12 months. There were 3 voting rounds, which were separated by periods for revision and discussion. The statements were rated with a 5-point scale including "totally disagree", "disagree", "neutral", "agree", and "totally agree". Consensus acceptance was defined as an agreement (Agree or Totally agree) by at least 80% of experts. A statement that reached this goal was accepted. The analyses of the results of the voting round were performed in a blind manner according to the I.D. of the participant. At the end of each round, the level of agreement was communicated to the panel as the percentage of agreement among experts. Experts were invited to comment disagreed statements through the MonkeySurvey® matrix. Statements returning with only 50–80% of agreement were revised regarding the expert's comments. Statements that did not reach at least 50% of agreement were discarded and were not subjected to additional revision and related voting. After the second voting round, a Teams® meeting (Microsoft®, Redmond, WA, USA) was organized with experts to further improve the remaining unvalidated statements.

Grades of evidence

The assignments of the grade of evidence to the statements were carried out by investigators with the GRADE system as is recommended for position/consensus papers [14]. The use of the GRADE system was important regarding the lack of high-level evidence in some areas of LPRD, which could indicate areas requiring future studies to improve LPRD guidelines. The grade of the statement aimed to give a practical indication of the likely impact of further research on confidence in the estimate effect [1, 14]. The following grade evaluations were evaluated 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.

Endorsement by the international federation of otolaryngology societies

The findings of the Delphi process through this publication were endorsed by the YO-IFOS, ELS, and the UEP of the CEORL-HNS as the "European Consensus Paper for Managing and treating LPRD".

Results and discussion

Thirty-six statements were validated. Twenty-four, 7, and 5 statements were validated after the first, the second, and the third rounds, respectively (Tables 2 and 3). Two statements were dedicated to the definition of LPRD, and two others were related to the HEMII-pH testing as gold standard for the diagnosis, which validated the IFOS consensus (Table 2) [1]. Among the 8 statements dedicated to the diagnosis, 4 focused on the role of the oropharyngeal pH monitoring in the management of LPRD, and the nasal/nasopharyngeal findings of LPRD. Two statements defined the place of the empirical therapeutic trial (Table 2). Of the 26 statements dedicated to the treatment, the diet and lifestyle recommendations and the primary medication were detailed in 9 and 7 statements, respectively. The management of recalcitrant LPRD, the weaning of medication, and the place of surgery were reported in 5, 3, and 2 statements, respectively (Table 3). The level of consensus increased through the successive voting rounds, with a higher level of consensus in the third round (Fig. 1).

Table 2 Statements for definitions and diagnosis

Statements	Agreement	*R*	EBM
Definition			
1. Laryngopharyngeal reflux has many alternative names including but not limited to: silent reflux, pharyngolaryngeal reflux, extraesophageal reflux, atypical GERD, reflux laryngitis, full column reflux, respiratory reflux, pharyngeal reflux and proximal reflux.	81.0%	1	A
2. Laryngopharyngeal reflux 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.*	100%	1	A
Diagnosis			
Hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing (HEMII-pH)			
3. When available, the gold standard approach to confirm the LPRD diagnosis is the 24-hour HEMII-pH.°	100%	1	A
4. The LPRD diagnosis can be confirmed for > 1 pharyngeal reflux event at the 24-hour HEMII-pH.	91.3%	1	B
Oropharyngeal pH-testing			
5. The oropharyngeal pH-monitoring (Restech) is an alternative procedure to support the LPRD diagnosis rather than the consideration of only symptoms and findings. However, future studies are needed to investigate the reliability of oropharyngeal-pH monitoring in comparison with the HEMII-pH, which is the gold standard.	91.3%	3	C
6. According to normative data study (see documents sent before starting the survey), the presence of > 10 pharyngeal reflux events at pH 6.0 at the oropharyngeal pH-monitoring can support the LPRD but future studies concurrently comparing Oropharyngeal pH-monitoring and HEMII-pH are needed to confirm the oropharyngeal pH-monitoring reliability.	87%	2	C
7. The lack of esophageal sensors allowing the demonstration of an esophageal full column prior to pharyngeal sensor detection is a limitation of oropharyngeal pH-monitoring, which limits its value towards HEMII-pH.	87%	2	B
8. Regarding the lack of esophageal-hypo-nasopharyngeal impedance-pH monitoring probe dedicated to nasal consequences of LPRD, the oropharyngeal pH-monitoring probe could be assessed in future studies with a nasopharyngeal placement of the sensor to document potential reflux event into the nasopharynx.	87%	3	D
Clinical Diagnosis and Empirical Therapeutic Trial			
9. If HEMII-pH is unavailable and laryngoscopic findings of LPRD are present, an empirical treatment covering acid, weakly acid and nonacid LPR may be prescribed and evaluated after at least one month; the empirical therapeutic trial being an alternative to support the LPRD diagnosis.	82.6%	1	B
10. Laryngoscopy, alone, is not sufficient for the diagnosis of LPRD. Some endoscopic characteristics (posterior commissure hypertrophy, laryngeal and arytenoid inflammation, vocal cord edema and erythema, ventricular band edema, endolaryngeal sticky mucus deposit, tongue tonsil hypertrophy, posterior oro/hypopharyngeal wall erythema) can support the clinical diagnosis but not confirm it.	87.0%	1	A

*IFOS Criteria. Abbreviations: GERD = gastroesophageal reflux disease; HEMII-pH: Hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing; LPRD = laryngopharyngeal reflux disease

Definition

The definition of LPRD was extensively discussed in the IFOS-Dubai consensus [1]. The validation of the two definitions statements of the IFOS-Dubai consensus aimed to ensure consistency between the international consensus and the European consensus (Table 2). Experts agreed to define LPRD 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. The backflow of gastroduodenal content (e.g., pepsin, bile acids, elastase, potentially trypsin) leads to the inflammation of the upper aerodigestive tract mucosa and the development of related symptoms. Recent studies strengthened the consideration of bile acids, elastase, and trypsin in the pathophysiology of LPRD; [15–18] these enzymes have been ignored in the past clinical and basic science research. The detection

Table 3 Statements for treating LPRD

Treatment			
Diet and lifestyle recommendations			
11. An anti-reflux diet and lifestyle advice addressing the anxiety, stress, or depression need to be recommended in patients with LPRD.	87.0%	1	B
12. The diet includes 1) the reduction of high-fat, high-released sugar, spicy foods/beverages, caffeine/theine beverages, alcohol, sparkling beverages, 2) the cook of raw vegetables, 3) the intake of high-protein foods.	91%	1	B
13. The patient can adhere to a standardized antireflux diet, which can improve its information and adherence.	91.3%	1	B
14. Alcohol consumption and tobacco smoking should be avoided in all patients with LPRD.	91%	1	B
15. Weight loss for overweight patients, elevating the head of the bed, lying left-side down, and avoidance late night meals and bedtime snacks can be recommended in patients with GERD. For LPRD, which is mainly gaseous, daytime and upright reflux, the usefulness of these lifestyle changes need to be evaluated in future studies considering LPRD patients.	91.3%	2	C
16. The antireflux diet and lifestyle advice can be recommended in the long-term given their benefits on cardiovascular and the overall health.	91.3%	1	B
17. The stress, anxiety, depression, and all psychological distress associated with an autonomic nerve dysfunction need to be addressed in the management of treatment.	95.7%	1	B
18. The evaluation of the psychological distress (e.g., anxiety, depression, perceived stress and insomnia) should be encouraged in non-responders.	87.0%	1	B
19. In case of sleep disorder and nighttime reflux disease, treatment with melatonin or melatonin receptor agonist should be evaluated in future studies regarding their effect on the baseline tonicity of the esophageal sphincter and the esophageal motility.	87.0%	2	D
Primary Medication			
20. In case of HEMII-pH or oropharyngeal pH-monitoring results, a personalized treatment can be prescribed considering the following characteristics of reflux: time of occurrence of events (daytime-upright, supine-nighttime); pH of events (acid (< 4), weakly acid (4–7), alkaline (> 7); and the presence of GERD (esophageal acid exposure time > 6% of time).	91.3%	1	B
21. Given the nature of most LPRD (weakly acid – alkaline), the use of alginate or magaldrate as main drugs of an empirical therapeutic trial is primarily recommended to address both acid and non-acid pharyngeal reflux events.	95.7%	1	B
22. Alginate and magaldrate are taken post-meals, at best 3 times daily, and, in case of nighttime reflux disease, at bedtime.	100%	1	B
23. Proton pump inhibitors (PPIs) are mandated for patients with GERD (Lyon criteria), GERD complications (esophageal stricture, Barrett metaplasia, ulcerative lesions), or GERD-related symptoms (acid brash, heartburn, regurgitations, non-cardiac chest pain).	100%	1	A
24. The duration of medication needs to be as short as possible to avoid medication-induced adverse events, PPI overprescription, and costs for healthcare systems.	95.7%	3	B
25. The minimal duration of treatment is between 2 to 3 months of an initial treatment.	81.8%	3	B
26. The use of validated patient-reported outcome questionnaire and clinical instruments documenting LPRD signs and symptoms at baseline and throughout treatment is recommended to evaluate the therapeutic responses due to the non-specificity of symptoms and findings.	95.7%	1	A
Treatment for recalcitrant reflux			
27. The lack of response can be based on the lack of significant change or worsening of patient symptoms at the patient-reported outcome questionnaire used at baseline.	82.6%	1	A
28. Non-responder patients to therapeutic lines need to be evaluated for compliance to medication, diet, and lifestyle advice.	95.7%	1	B
29. Patients without partial or total symptom relief after 2 months of treatment need to continue the treatment to achieve a therapeutic period of 3 months.	82.6%	1	C
30. Practitioner can consider changing medication (molecule family or galenic) in primary non-responder patients.	95.7%	2	C
31. The treatment regimen can be changed/tailored every 3 months after the first posttreatment evaluation.	87.0%	1	C
Weaning and Reduction of Medication			
32. The stop of PPIs can be degressive according to the risk of rebound effect.	82.6%	1	B
33. According to the potential risk of reported adverse events (e.g., osteoporosis, increased risk of malabsorption, pneumonia, Clostridium Difficile colitis) and the costs for healthcare system, the prescription of long-term PPIs is not recommended for patients without severe GERD-complications or uncontrolled symptoms with proven GERD	95.7%	3	B

Table 3 (continued)

Treatment			
34. The progressive reduction of alginate or magaldrate can help patients with partial or total symptom reliefs to stop treatment (weaning), while reducing the risk of recurrence.	87.0%	1	C
Surgery			
35. Fundoplication is an alternative therapeutic option for patients with GERD objective diagnosis, severe GERD-related symptoms, and hiatal hernia irrespective to the presence of LPRD.	100%	2	A
36. Practitioner should inform patient that the effectiveness of fundoplication on LPRD symptoms is unexpectable.	95.7%	2	B

Abbreviations: GERD = gastroesophageal reflux disease; HEMII-pH: Hypopharyngeal-oesophageal multichannel intraluminal impedance-pH testing; LPRD = laryngopharyngeal reflux disease

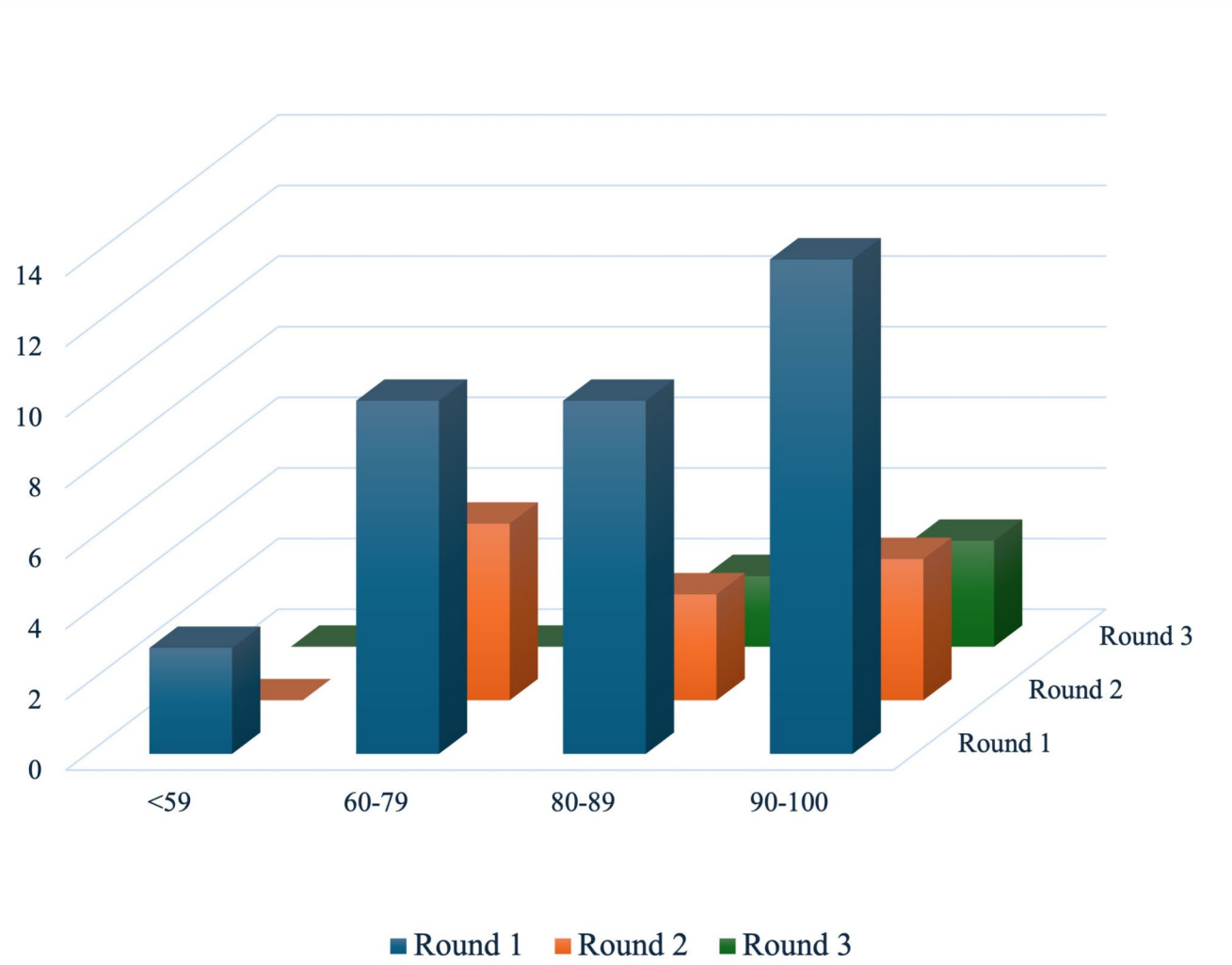

Fig. 1 Validation of statements in the three rounds. In the first round, 14, 10, 10, and 3 statements had 90–100%, 80-89.9%, 60–79%, and < 59.9% of agreements. In the second round, 4, 3, and 5 statements reached 90–100%, 80-89.9%, and 60–79% of agreements. In the third round, 3 and 2 statements reached 90–100%, and 80-89.9% of agreements, respectively. Note that some statements were merged into a single statement for the next round

of bile acids, elastase, and trypsin in the saliva of LPRD patients supports the occurrence of dysmotility mechanisms in the upper digestive tract with reflux processes from the duodenum to the stomach and, as demonstrated in HEMII-pH studies [19, 20], from the stomach to the esophagus and pharynx. The dysmotility is assumed to be associated with an autonomic nerve dysfunction, which can develop in patients with anxiety, stress, or depression [21–23]. The documentation of gastroduodenal enzymes into anatomical regions out of the larynx and pharynx, e.g., sinonasal regions [4, 24],

middle ear [25], tracheobronchial tube [26], or tears [27] can support an emerging debate about the consistency of the term "laryngopharyngeal reflux", which could be renamed "airway reflux" in the future [28].

Diagnosis

Hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring

The detection of gastroduodenal enzymes into the upper aerodigestive tract mucosa, and the related documentation of mucosa/cell injuries, clinical signs, and symptoms of LPRD [29, 30] make important the detection of backflow of gastroduodenal content into the pharynx. Thus, experts considered the 24-hour HEMII-pH as the gold standard for detecting full column (gastro-esophago-pharyngeal reflux event) and validated the IFOS-Dubai consensus criteria of more than one pharyngeal reflux events for confirming the diagnosis [1]. This threshold has been proposed in a recent systematic review of normative data studies for HEMII-pH, MII-pH, or oropharyngeal-pH monitoring [31]. In this paper, the authors reported that the mean and the 95th percentile thresholds of hypopharyngeal reflux event at the 24-hour HEMII-pH among healthy individuals were 1, and 0 to 10, respectively [31]. When the pH-impedance probe does not have a pharyngeal sensor, the 95th percentile thresholds were 10 to 73 events for proximal esophageal reflux events [31]. In the present consensus paper, the authors emphasized that only probes with esophageal and pharyngeal impedance/pH sensors can reliably confirm the diagnosis. Indeed, a significant number of proximal esophageal reflux events do not reach the pharynx due to the protective contraction of the upper esophageal sphincter [32]. The aforementioned normative data study also suggested that the 95th percentile of pharyngeal reflux events was 40 to 128 for events with pH < 6.0 at the 24-hour oropharyngeal-pH monitoring, which highlights the occurrence of substantial differences across devices in the sensitivity to detect pharyngeal reflux events [31]. In the present study, experts agree to consider oropharyngeal-pH testing as an adjunctive tool in cases where HEMII-pH are lacking, while the diagnosis can be confirmed with more than 10 pharyngeal reflux events at pH 6.0 (Statement 6; Table 2). However, the experts did not consider the oropharyngeal pH monitoring as a gold standard for the LPRD diagnosis for many reasons. First, the detection of full column at the 24-hour HEMII-pH is important to exclude any false positive event, which can be defined as a pseudo-event related to probe movement, or dryness. The single oropharyngeal sensor of the oropharyngeal-pH monitoring and the lack of identification of the proximal esophageal event before the detection of the pharyngeal reflux event is the primary limitation of oropharyngeal-pH monitoring given its inability to detect pseudo-reflux event [33]. Despite this limitation, experts believe that future studies are needed to investigate the accuracy of oropharyngeal-pH monitoring in patients who simultaneously underwent HEMII-pH (gold standard) and oropharyngeal-pH monitoring during the same 24-hour period. This kind of study is important to investigate the correlation between pharyngeal reflux events detected by HEMII-pH and oropharyngeal-pH monitoring. Fuchs et al. simultaneously performed single-probe pH monitoring and oropharyngeal-pH monitoring in patients with suspected LPRD [34]. The authors reported a mismatch between both approaches in the reflux diagnosis, but they used a single-probe esophageal-pH monitoring and based the LPRD diagnosis on the DeMeester score, which is inconsistent with the current consensus [34]. Recently, Vance et al. compared the diagnostic value of 24-hour HEMII-pH and oropharyngeal-pH monitoring in patients with LPRD symptoms and findings [35]. The authors did not find a strong association between the detection of pharyngeal events at the 24-hour HEMII and the oropharyngeal-pH monitoring. Precisely, the HEMII-pH detected more events of pH < 4 than oropharyngeal-pH testing, while oropharyngeal-pH testing detected more total events and recorded longer event times than HEMII-pH [35]. Note that patients did not have both pH procedures in the same 24-hour period, which can be a significant bias given the potential day-to-day variability of reflux events at the pH testing [19]. Finally, experts did not propose the Ryan score for suggesting the LPRD diagnosis at the oropharyngeal-pH monitoring because the Ryan score only considers acid pharyngeal events excluding weakly acid or alkaline reflux events (pH > 5.5), [36] which is inconsistent with the current knowledge of the LPRD profile [19, 20]. Future studies using a 48-hour or 72-hour testing period are needed to confirm both HEMII-pH and oropharyngeal pH-testing criteria proposed in the present consensus addressing the day-to-day variability issue. Finally, given its configuration (single probe) and the ease of placing the probe, experts suggested that future studies could be conducted to evaluate the place of oropharyngeal pH testing in the detection of nasopharyngeal or nasal reflux disease.

Empirical treatment diagnosis

The HEMII-pH or oropharyngeal-pH monitoring are not available in all centers. Thus, most practitioners make a clinical diagnosis of LPRD based on symptoms, findings, and their evolutions throughout an empirical therapeutic trial [37, 38]. In the present consensus, experts agreed to propose the empirical therapeutic trial as an alternative approach for

suggesting the LPRD diagnosis (Statement 9, Table 2). This approach can be cost-effective for patients with mild-to-moderate LPRD [1, 11]. Regarding the weakly acid or alkaline profile of most LPRD at the 24-hour HEMII-pH [19, 20, 39], the experts encourage practitioners to prescribe an empirical treatment covering acid, weakly acid, and alkaline reflux events, such as post-meal alginate or antacids (Statement 21, Table 3). A minimal duration of two months was proposed for the empirical treatment given studies showing that most symptoms (reflux symptom index) were mainly relieved after 1-to-2 months of treatment [40–43]. Given the non-specificity of symptoms and signs associated with LPRD, experts recommended evaluating the effectiveness of the treatment with patient-reported outcome questionnaires and validated clinical tools. This recommendation matches with the recent guidelines for the voice quality assessment of the ELS and UEP [44], where experts proposed to evaluate the symptoms and findings of LPRD with reflux symptom score (RSS) [45] and reflux sign assessment (RSA) [46]. RSS, RSS-12, RSA, and RSA-10 are all European reliable and validated clinical instruments to document LPRD symptoms and findings [1, 11, 45–47].

Treatments

To date, there is no international consensus for treating LPRD. The IFOS-Dubai consensus defined and proposed a practical management for the diagnosis of LPRD but there was no recommendation for the treatment of patients with primary and recalcitrant LPRD [1]. In the present consensus paper, 9, 15, and 2 statements were dedicated to the management of the etiological factors (diet, stress, anxiety, and depression), the medical treatment, the indications of surgery (fundoplication), and the management of recalcitrant patients (Table 3).

Diet and lifestyle changes

The number of studies dedicated to the relationship between LPRD, foods, and beverages has significantly increased in the past few years [48–55]. The first studies conducted by Koufman e*t al* [53, 55]. proposed a low-acid, low-fat, alkaline water, and high-protein diet to treat patients with primary or recalcitrant LPRD. The anti-acid diet of Jamie Koufman aimed to primarily act on the acidity of gastric content to neutralize the pepsin activity in the upper aerodigestive tract mucosa [11, 53, 55]. Recently, two studies reported that patients consuming acid, high-fat, and low-protein diets had higher pharyngeal reflux events at the 24-hour HEMII-pH [52], or higher saliva pepsin concentration [53]. Another investigation showed that the adherence to an anti-acid, low-fat, high-protein, and low-high released sugar diet was associated with 54% symptom relief at 3 months post-treatment [49], which corroborated the results of Zalvan et al.. who reported similar symptom relief in patients treated with Mediterranean diet *versus* PPIs [54]. These recent studies supported that the effectiveness of the diet is related to the impact of the food and beverage compositions on the gastroesophageal physiology rather than an anti-acid effect. Indeed, fatty meals and raw vegetables increase the gastric emptying time, which can increase the number of transient relaxation of the low esophageal sphincter [56]. Proteins have been suggested to increase the lower and upper sphincter tonicities, whereas caffeine, theine, tobacco, spicy foods, and alcohol do the opposite [56]. The consumption of sparkling beverages and the related eructation (refluxed CO_2 droplets) can lead to the deposit of gastroduodenal content (enzymes) into the upper aerodigestive tract mucosa [56]. Unlike GERD, patients with LPRD are not obese [57, 58], and the pharyngeal reflux events occur daytime and upright [19, 20]. These findings support statement 15 where experts do not validate weight loss and the elevating of the head of the bed in LPRD patients because these recommendations are more adapted to GERD. In clinical practice, adherence to the anti-reflux diet is important to reach a high probability of weaning rate of all medication over the long term, while controlling LPRD symptoms [60].

Lifestyle has been suggested as an etiological or contributing factor of LPRD [21–23, 61]. The well-known relationship between LPRD and autonomic nerve dysfunction led investigators to propose statements related to lifestyle changes and psychological distress (Table 3) [21–23]. The management of stress [21, 22], anxiety [62], depression [23, 61], and sleep disturbance [62] is mandated to improve patient care, especially when the symptoms are recurrent or chronic. Experts thought that future studies are needed to evaluate the interest of melatonin in patients with both LPRD and sleep disturbance given its anti-inflammatory role and its positive impact on the tone of the esophageal sphincters [63]. Lifestyle changes and the adherence to an anti-reflux diet can reduce the consumption of medications, and, in addition, they can have a significant impact on cardiovascular health [54].

Medical treatment

The medical treatment strategy needs to consider that most LPRD patients have upright, daytime, and weakly acid or alkaline pharyngeal reflux events at the 24-hour HEMII-pH [19, 20]. However, the profile of the disease can be influenced by the presence of GERD, being overweight, or diet habits [64]. In this way, experts recommend a personalized treatment depending on the reflux profiles at the 24-hour HEMII-pH (statement 20). This statement was supported

by studies reporting higher therapeutic success rates in patients treated with personalized therapy compared to those who were treated by PPIs or standardized approaches [65, 66]. To date, the superiority of PPIs over placebo has not been demonstrated in LPRD [12], which can be attributed to the weakly acid or alkaline profile of the disease. The lack of effectiveness of PPIs in LPRD led experts to limit the indications of PPIs to patients with GERD findings and to decrease PPIs progressively to avoid the rebound effect (Table 3). Weakly acid and alkaline pharyngeal reflux events can be adequately treated with alginates and antacids. Sodium alginate or alternative alginate forms a barrier above the gastric content that significantly reduces the gastroesophageal reflux events, and, consequently, the probability for events to reach the upper aerodigestive tract [67]. Antacids neutralize acid in the stomach and esophagus and lead to the chelation of pepsin and bile salts, which cannot reach the pharynx [68]. Currently, only a few studies investigated the effectiveness of alginate as primary therapy for LPRD patients [69, 70], while there is no study investigating antacids as a single medication for treating LPRD. Thus, the statements proposing alginate or antacid (e.g., magaldrate) for the treatment of LPRD are mainly based on the current knowledge of the LPRD pathophysiology, and a few uncontrolled studies where the combination of PPIs, alginate, or magaldrate led to higher therapeutic success rates compared to PPI-based studies [65, 66, 71]. Future controlled randomized studies are however needed to determine the best empirical pharmaceutical combination.

Recalcitrant reflux, weaning, and surgery

The management of recalcitrant LPRD and the weaning of medication are both seminal to this consensus paper. Symptom relief can be observed after 1- to 2 months of treatment, leading experts to consider a therapeutic period of 2 months as the standard of care. Practitioners can change drug classes rather than increase doses in cases of lack of symptom changes after 2 months [72]. The change of drug classes for recalcitrant LPRD is supported by a recent study demonstrating that the change of medication classes was an effective approach in resistant patients to a primary therapeutic regimen [72]. The change of drug classes is an alternative approach to the increase of drug doses, which reports controversial results [72]. The experts recommended reducing the medication doses in patients with partial or total relief of symptoms (Table 3). This recommendation can reduce the cost for healthcare systems [73, 74] and the potential adverse events of long-term high-dose medication [75]. Weaning the LPRD medications can be possible in 66–69% of LPRD patients [59, 76]. In the present consensus paper, the experts proposed fundoplication only for patients with GERD findings, which was based on the unpredictable success of fundoplication in patients with LPRD symptoms only [77]. However, determining the indication for fundoplication in reflux diseases was not the purpose of the paper, and that requires future studies.

Conclusion

A European consensus endorsed by the CEORLHNS societies is presented to improve the management and treatment of LPRD. The approved statements could improve collaborative research through the adoption of common management approaches to LPRD. Future clinical studies using the recommendations of the present consensus are needed to evaluate its accuracy and provide future evidence-based medicine improvements.

Author contributions Study concept and design: Lechien, Hans, Chiesa-Estomba, Nacci. Acquisition, analysis, or interpretation of data. Lechien, Schindler, Bohlender, Runggaldier, Crevier-Buchman, Oguz, Zelenik, Tedla, Siupsinskiene, Schlomicher-Their, Taimrova, Karkos, Geneid, Dapri, Muls, Aoun, Cammaroto, Vaira, Saibene, Iannella, Mayo-Yanez, Weitzendorfer, Savarino, Remacle, Maniaci, Barillari. Drafting of the manuscript. Lechien, Maniaci, Barillari. Critical revision of the manuscript for important intellectual content: all authors.

Funding None.

Declarations

Ethic committee No IRB approval was required for this study protocol.

Informed consent Participants consented to the study.

Competing interests The author Jerome R. Lechien was not involved with the peer review process of this article.

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