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ORIGINAL ARTICLE

Best Practices in Treatment of Laryngopharyngeal Reflux Disease: A Multidisciplinary Modified Delphi Study

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Abstract

Background Laryngopharyngeal reflux (LPR) is a common otolaryngologic diagnosis. Treatment of presumed LPR remains challenging, and limited frameworks exist to guide treatment.

Methods Using RAND/University of California, Los Angeles (UCLA) Appropriateness Methods, a modified Delphi approach identified consensus statements to guide LPR treatment. Experts independently and blindly scored proposed statements on importance, scientific acceptability, usability, and feasibility in a four-round iterative process. Accepted measures reached scores with ≥ 80% agreement in the 7–9 range (on a 9-point Likert scale) across all four categories.

Results Fifteen experts rated 36 proposed initial statements. In round one, 10 (27.8%) statements were rated as valid. In round two, 8 statements were modified based on panel suggestions, and experts subsequently rated 5 of these statements as valid. Round three's discussion refined statements not yet accepted, and in round four, additional voting identified 2 additional statements as valid. In total, 17 (47.2%) best practice statements reached consensus, touching on topics as varied as role of empiric treatment, medication use, lifestyle modifications, and indications for laryngoscopy.

Conclusion Using a well-tested methodology, best practice statements in the treatment of LPR were identified. The statements serve to guide physicians on LPR treatment considerations.

Keywords Laryngopharyngeal reflux · Gastroesophageal reflux · Delphi

Introduction

In contrast with gastroesophageal reflux disease (GERD), laryngopharyngeal reflux (LPR) describes the retrograde flow of gastroduodenal contents into the larynx and pharynx, where it can lead to symptoms including hoarseness, sore throat, chronic cough, dysphonia, globus, and throat clearing [1]. The prevalence of LPR is unknown due to lack of agreed diagnostic criteria but is believed to be a factor contributing to laryngopharyngeal complaints in as many as 50% of patient visits to otolaryngologists [2].

Despite advances in the diagnosis of LPR, including stroboscopy and pharyngeal pH-impedance probes, empiric anti-reflux treatment remains the most common management approach.

A significant proportion of patients with presumed LPR do not respond to acid-only therapies such as proton pump inhibitors (PPIs) [3, 4]. This is in contrast with GERD, where PPIs routinely offer symptom control and resolution of acid-related esophageal mucosal damage. Further, laparoscopic Nissen fundoplication is a well-established and reliable surgical treatment in GERD, whereas the role of fundoplication in treatment of LPR remains less conclusive [5]. Because the response of LPR to traditional GERD therapies has been relatively disappointing, treatment of LPR remains challenging and sometimes controversial. This leaves many primary care providers, pulmonologists, gastroenterologists, otolaryngologists, and general surgeons to manage symptoms as best they can without a framework to guide best

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practices in treatment of LPR. Well-developed, scientifically supported guidance on LPR treatment may therefore be useful for managing these patients in clinical practice.

The aim of this study was to develop consensus statements on how to treat patients with known or suspected LPR. Consequently, an expert panel participated in an iterative modified Delphi process. Emphasis was on multidisciplinary collaboration, and therefore experts chosen included Otolaryngologists, Gastroenterologists, and General Surgeons who specialize in the management of GERD and its complications.

Methods

To develop an expert-based consensus statement on treatment strategies in LPR, the RAND/University of California, Los Angeles Delphi Appropriate Methodology (RAM) was applied through a modified, four-round Delphi technique using invited academic otolaryngologists, gastroenterologists, and general surgeons who specialize in management of gastroesophageal reflux disease. All included experts receive patients in tertiary settings for the management and treatment of gastroesophageal reflux disease. The Delphi process was organized by an investigator (AK) who was not herself a voting member of the panel. Senior authors (TC and LA) wrote the initial statements to guide voting and were also non-voting members of the study team. This study was approved by the Stanford University Institutional Review Board (IRB). Patients or the public were not involved in the design or dissemination of this research, due to the nature of this project seeking a consensus among experts in the field.

Compilation of Potential Consensus Statements

A consensus statement is defined as a comprehensive analysis created by a panel of multidisciplinary experts that advances understanding of a disease, regarding diagnosis or treatment. Potential consensus statements were initially conceived by the senior authors after an extensive literature review including large randomized clinical trials, cohort studies, systemic reviews, and professional society guidelines.

The primary investigators aimed to develop potential consensus statements that were focused on issues regarding solely the treatment of LPR. Candidate consensus statements included topics on proton pump inhibitors (PPI), histamine-2-antagonists (H2RA), alginate-based barrier forming agents (alginates), lifestyle modifications, laryngoscopy, endoscopic and surgical treatment, and the role of empiric treatment prior to objective testing. After an extensive literature review, the primary investigators composed 36 initial consensus statements, with the intention that this list be further modified, and statements removed and/or edited, based on subsequent expert suggestions and voting.

Expert Panel Recruitment

A panel of 15 experts were invited to participate by direct email invitation from the primary investigators. Experts were recruited based on their national and/or international reputation of their expertise in treating LPR and on their publications and academic record within their individual fields of otolaryngology, gastroenterology, and general surgery. To achieve generalizability of the developed consensus statements, 3 international experts with English language proficiency and academic health systems similar to that of the United States were included. All 15 experts recruited accepted the invitation and were enrolled into round one of the study.

Analyzing Consensus Statements for Validity

For each proposed consensus statement, voting panelists applied a scoring system adapted from standard quality indicator development [6–8]. Surveys were sent to each voting panelist through Qualtrics (Qualtrics, Provo, UT) and responses were collated on-line. For each individual statement, a distinct score for each of four separate categories was collected. A 9-point Likert scale was used in which a score of 1 = "definitely not valid," 5 = "uncertain," and 9 = "definitely valid." The four categories in which each statement was scored were *importance, scientific acceptability, usability, and feasibility* (Table 1).

Proposed statements were scored based on degree of agreement within the same three-point range (i.e., 1–3, 4–6,

Table 1 Category names and respective definitions

Independent categories	Definitions
Importance	Will this make significant gains to improve health care outcomes?
Scientific acceptability	Is this based on scientific evidence?
Usability	Is this meaningful, understandable, and useful; can providers understand the results and find them useful for decision making?
Feasibility	Will this minimize burden; is data collection and implementation of results feasible?

or 7–9). For a statement to be considered acceptable, all 4 categories for that individual statement (e.g., importance, scientific acceptability, usability, and also feasibility) each had to achieve ≥ 80% of scores within the three-point range between 7 and 9 [6–8].

Importantly, statements incorporated modifiers to the word "LPR" when describing the certainty of a reflux diagnosis as cause for the patient's symptoms. Statements that refer to patients with "suspected LPR" indicate those for whom reflux is suspected based on initial complaints, but without any further confirmatory signs or symptoms; this is the category of patients for whom reflux is least well established as actual cause for patient complaints. Those with "presumed LPR" are those in whom concomitant GERD complaints further increase an index of suspicion for reflux as etiology for laryngopharyngeal complaints, and/or those in whom laryngopharyngoscopy does not identify non-reflux etiologies for patient complaints—that is to say, "presumed" LPR patients are those for whom there is a higher index of suspicion that reflux is the actual cause of patient complaints than those with "suspected" LPR. Finally, as used in these recommendations, "demonstrated reflux" patients are those for whom objective testing and/or response to medication trials have more conclusively demonstrated that reflux is indeed the cause of a patient's laryngopharyngeal complaints (Fig. 1).

Round 1: Initial Scoring of LPR Treatment Strategies

In round one, members on the expert panel received email instructions on how to access the voting round hosted by Qualtrics. Experts were provided with instructions and definitions of the 4 independent categories—*importance, scientific acceptability, usability, and feasibility*—to ensure all voting panelists interpreted the terms similarly (Table 1). In addition to scoring each proposed statement using each of the four categories described above, all participants were given an opportunity to suggest modifications to the wording of the statement, or to clarify the meaning of the statement, with a blank text response field. Applying the scoring criteria, all statements were analyzed to determine the degree of agreement and whether the proposed statements would be accepted, deleted, or included with or without suggested modifications into round two.

Following round one of the Delphi process and per the established methodology, statements with ≥ 80% of expert scores for each of the 4 criteria within the three-point range between 7 and 9 were 'accepted.' Statements with rankings falling below 7–9 in all four separate categories, on the other hand, were discarded from further discussion. The remaining statements had intermediate overall scores, reaching the ≥ 80%, 7–9 score for some, but not all, of the categories. These "intermediate score" statements were edited by non-voting members of the study team (AK, TC, and LA) based on the suggestions from the free text responses in order to re-shape the statements into revised forms that were then subjected to further voting in round two.

Round 2: Re-scoring of LPR Treatment Strategies

In round two, the experts were asked to score those statements which had achieved intermediate scores in round one and which had been subsequently modified by non-voting members of the panel. Statements that had already been accepted or discarded based on initial round one scores were not presented in this subsequent round. Experts were instructed to independently re-score the revised statements applying the same 9-point Likert scale across each of the same 4 categories used previously. Applying the same scoring criteria, all included statements were re-analyzed

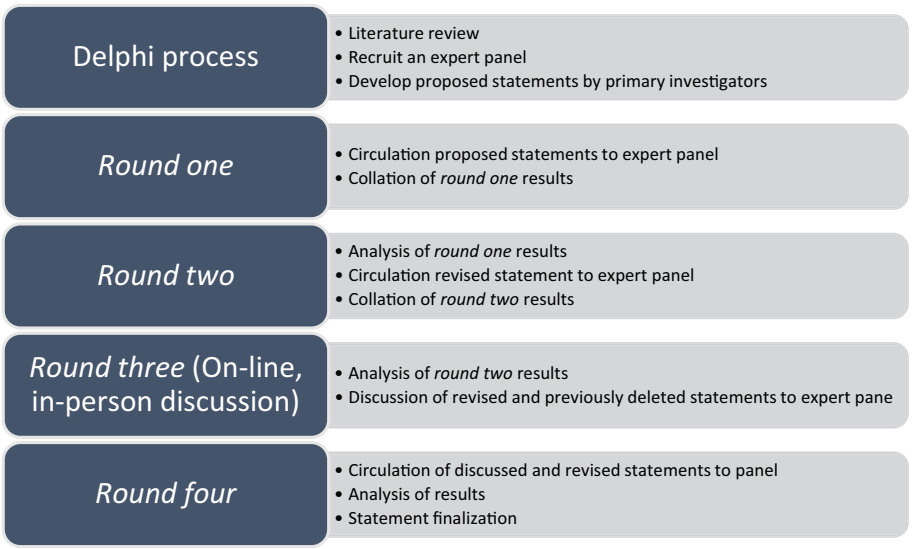

Fig. 1 Overview of Delphi consensus statement development of treatment strategies in LPR

to determine degree of expert agreement. Using the same stratification thresholds as had been used after the initial voting round, some statements were considered to have reached consensus and were accepted, some statements were discarded, and others with persistently intermediate scores were advanced into *round three for further discussion.*

Round 3: Video Conference Discussion

After the two rounds of questions, experts were invited to participate in a real-time, on-line virtual discussion hosted by Zoom Video Communications (San Jose, CA, USA). Prior to the meeting, each expert was provided their own ratings from the preceding two rounds as well as de-identified overall group ratings. Experts did not vote on statements during round 3; instead, this round functioned as a platform for open discussion among experts. Experts were provided an opportunity to freely discuss items that had met with agreement, were deleted, or that had intermediate scores after the first two voting rounds. Experts were then given the opportunity to provide suggested modifications to wording and sentence structure that would be incorporated into the final round four statements.

Round 4: Final Rankings of LPR Treatment Strategies

Following round three discussion, statements were modified by non-voting members (TC, LA, and AK) based on the expert suggestions. In the final round, experts independently re-scored 4 remaining statements. Re-scored statements included 3 that had been re-worked due to persistent intermediate scores in round two and then re-worded in round three, and 1 additional statement that had been previously discarded in an earlier round due to meeting low agreement in all four categories but which was able to be more effectively re-worded for further voting based on comments from the experts.

Results

A total of 15 recognized specialists including gastroenterologists ($n=5$), otolaryngologists ($n=8$), and general surgeons ($n=2$) from four countries (United States, New Zealand, France, and Italy) were voted initially on 36 statements concerning treatment of LPR. In round one, there was a consensus of agreement indicating high validity for each of the four categories (importance, scientific acceptability, usability, and feasibility) for 10 statements, consensus scores indicating low validity for 20 statements for all 4 categories, and 6 statements with intermediate scores (Table 2). These statements were then re-worded. Additionally, free text responses led to the generation of 2 additional items. Therefore, a total of 8 statements were transferred to round two for re-voting.

In round two, there was a consensus agreement on 5 of the 8 statements and a consensus low score on zero statements. The expert panel was unable to reach consensus on the remaining 3 statements (Table 2). These 3 statements were then placed on the agenda to discuss in the round three video conference portion of this iterative process.

All three non-voting study team members and nine of the 15 voting experts attended virtual real-time, on-line discussion in round three. Additional comments from those who could not attend the videoconference session were read aloud by the moderators. The expert panel discussed the three statements not reaching consensus in the second round, as well as 1 statement that did not meet consensus agreement in round one. The group suggested one question be separated into two separate questions and then subject to re-voting, a reflection of different treatment options offered by surgeons and advanced gastroenterologists. Ultimately, in round four, the expert panel completed a final vote on a total of 5 proposed statements. The result of round 4 voting was a consensus on 2 statements and disagreement on 3 statements.

In total, after completing a four-round Delphi method, the expert panel agreed with a consensus on 17 out of the initial 36 (47.2%) proposed statements. These statements relate to lifestyle modification ($n=2$), role of laryngoscopy ($n=2$), proton pump inhibitors ($n=4$), endoscopic treatment and surgery ($n=4$), and overall treatment approaches with specific regard to the role of empiric treatment ($n=5$). A full list of these statements reaching consensus, along with their final scores for each of the 4 criteria for acceptability, is found in Tables 2 and 3.

Statements Meeting Consensus (Table 2)

Lifestyle Modification

1. *If a patient has suspected, presumed, or demonstrated LPR, then recommending dietary and lifestyle modifications can be an effective part of an overall treatment approach.*
2. *If a patient has suspected LPR with mild complaints, then dietary and lifestyle modifications may be considered as an initial step in care without additional medication.*

Lifestyle modifications or changes, the same as those used to mitigate GERD symptoms, are often a first-line treatment for presumed LPR. For GERD, studies have suggested that weight loss, head of bed elevation, and avoiding meals within 2–4 h of bedtime lead to decreased esophageal acid exposure and improved symptom management [9]. However, there are limited data available when it comes to understanding the

Table 2 Questions reaching agreement on importance, scientific acceptability, usability and feasibility

Statement categories	
Lifestyle modification	1. If a patient has suspected, presumed, or demonstrated LPR, then recommending dietary and lifestyle modifications can be an effective part of an overall treatment approach
	2. If a patient has suspected LPR with mild complaints, then dietary and lifestyle modifications may be considered as an initial step in care without additional medication
Laryngoscopy	3. If a patient has LPR symptoms without classic GERD complaints, then work-up should include laryngopharyngoscopy
	4. If a patient with suspected or presumed LPR has concomitant voice complaints that do not improve with reflux treatment, then referral for laryngoscopy and/or laryngeal videostroboscopy is indicated
Proton pump inhibitor (PPI)	5. If a patient with presumed LPR whose symptoms respond to initial acid suppression treatments cannot later be weaned from medication without symptom recurrence, then titrate to lowest dose of PPI or H2 antagonist needed for long-term symptom control or consider other options for long-term reflux control
	6. If a patient with presumed or demonstrated LPR is taking PPI with improvement in symptoms, then inform patient of reported risks of long-term PPI use and offer alternative treatments if the patient does not want to be on PPIs long-term
	7. If PPIs are chosen for use in LPR treatment, then they should be dosed 30–60 min before meals
	8. If a patient is prescribed PPIs for LPR empiric treatment, then risks and benefits of PPI use should be reviewed with the patient carefully prior to use
Endoscopic treatment and surgery	9. If a patient is being considered for endoscopic or surgical reflux treatment, then a thorough pre-procedure evaluation should be performed to assess esophageal function as part of treatment planning
	10. If a surgeon is considering fundoplication for a patient with LPR symptoms in the absence of GERD, then otolaryngologic evaluation is warranted prior to any surgery in order to assess for non-reflux etiologies contributing to patient symptoms
	11. If a patient is being considered for endoscopic treatment of LPR, then they should be counseled that its efficacy in LPR patients is not completely understood
	12. If a patient with LPR demonstrates good symptom control with medications, then with supportive objective reflux and motility testing, a surgical anti-reflux procedure may be considered as an alternative to continued medication
Philosophy and/or empiric treatment	13. If a patient with presumed LPR responds to initial treatment but has persistent complaints even when titration/addition of medication has reached a plateau, then objective testing such as pH-impedance reflux testing can be pursued to help identify refractory reflux or suggest, if reflux is adequately controlled, that non-reflux etiologies for patient complaints need to be considered
	14. If a patient with presumed LPR has reached therapeutic plateau with reflux treatment and still has persistent symptoms, then consider evaluation of non-reflux etiologies for common complaints such as globus pharyngeus, cough, throat clearing, hoarseness, etc., that had previously been attributed to LPR
	15. If a patient is sent for objective reflux testing, then the referring physician should think critically about testing on therapy vs off therapy relative to interpretation of results
	16. If a patient with suspected LPR does not have any response to an adequate empiric trial of antacid medication, then objective testing such as pH-impedance and high-resolution esophageal manometry testing can be pursued to help identify refractory non-acidic or weakly acidic reflux or to suggest that etiologies other than reflux for patient complaints need to be considered
	17. If a patient is being treated for LPR, then approaches to evaluation and management should take into account factors such as symptom severity and patient-related factors such as age, health status, and co-morbid conditions

effect of these lifestyle changes on LPR. Recent studies have demonstrated that patients with LPR who consume high-fat, low-protein, high-sugar, and acidic foods and beverages experience significantly higher numbers of proximal reflux events as measured by pH-impedance catheters [10]. Early small studies reported that a strict low acid diet resulted in a significant reduction in reflux symptom index (RSI) and reflux finding score (RFS), scoring systems for symptoms and signs of LPR, respectively [11]. Similarly, a prospective cross-over study found that patients with pH-impedance proven LPR that followed a low-fat, low-quick-release sugar, high-protein, alkaline, and plant-based diet reported significant symptom relief [12]. Recognizing the limited data, the authors do not necessary recommend all patients must begin on a restrictive diet, but view dietary modification as a possibility based on the patient's goals.

Other than diet, consumption of alkaline water has also been explored as an option to treat LPR. In vitro studies demonstrate alkaline water (pH > 8) can deactivate pepsin [13]. However, a more recent study where alkaline water

Table 3 Best practice statements deemed to be valid by consensus opinion from 15 experts using four-round Delphi technique

Best practice statement	Agreement (%)			
	Importance (%)	Scientific acceptability (%)	Usability (%)	Feasibility (%)
If a patient has suspected, presumed, or demonstrated LPR, then recommending dietary and lifestyle modifications can be an effective part of an overall treatment approach	93.3	86.7	93.3	86.7
If a patient has suspected LPR with mild complaints, then dietary and lifestyle modifications may be considered as an initial step in care without additional medication	93.3	80.0	93.3	80.0
If a patient has LPR symptoms without classic GERD complaints, then work-up should include laryngopharyngoscopy	100	100	93.3	93.3
If a patient with suspected or presumed LPR has concomitant voice complaints that do not improve with reflux treatment, then referral for laryngoscopy and/or laryngeal videostroboscopy is indicated	100	93.3	100	100
If a patient with presumed LPR whose symptoms respond to initial acid suppression treatments cannot later be weaned from medication without symptom recurrence, then titrate to lowest dose of PPI or H2 antagonist needed for long-term symptom control or consider other options for long-term reflux control	86.7	80.0	93.3	93.3
If a patient with presumed or demonstrated LPR is taking PPI with improvement in symptoms, then inform patient of reported risks of long-term PPI use and offer alternative treatments if the patient does not want to be on PPIs long-term	93.3	86.7	100	93.3
If PPIs are chosen for use in LPR treatment, then they should be dosed 30–60 min before meals	86.7	93.3	93.3	93.3
If a patient is prescribed PPIs for LPR empiric treatment, then risks and benefits of PPI use should be reviewed with the patient carefully prior to use	100	93.3	93.3	100
If a patient is being considered for endoscopic or surgical reflux treatment, then a thorough pre-procedure evaluation should be performed to assess esophageal function as part of treatment planning	100	100	86.7	86.7
If a surgeon is considering fundoplication for a patient with LPR symptoms in the absence of GERD, then otolaryngologic evaluation is warranted prior to any surgery in order to assess for non-reflux etiologies contributing to patient symptoms	86.7	80.0	86.7	86.7
If a patient is being considered for endoscopic treatment of LPR, then they should be counseled that its efficacy in LPR patients is not completely understood	93.3	93.3	93.3	93.3
If a patient with LPR demonstrates good symptom control with medications, then with supportive objective reflux and motility testing, a surgical anti-reflux procedure may be considered as an alternative to continued medication	93.3	93.3	93.3	93.3
If a patient with presumed LPR responds to initial treatment but has persistent complaints even when titration/addition of medication has reached a plateau, then objective testing such as pH-impedance reflux testing can be pursued to help identify refractory reflux or suggest, if reflux is adequately controlled, that non-reflux etiologies for patient complaints need to be considered	100	86.7	80.0	80.0
If a patient with presumed LPR has reached therapeutic plateau with reflux treatment and still has persistent symptoms, then consider evaluation of non-reflux etiologies for common complaints such as globus pharyngeus, cough, throat clearing, hoarseness, etc. that had previously been attributed to LPR	100	100	100	100
If a patient is sent for objective reflux testing, then the referring physician should think critically about testing on therapy vs off therapy relative to interpretation of results	100	86.7	86.7	86.7
If a patient with suspected LPR does not have any response to an adequate empiric trial of antacid medication, then objective testing such as pH-impedance and high-resolution esophageal manometry testing can be pursued to help identify refractory non-acidic or weakly acidic reflux or to suggest that etiologies other than reflux for patient complaints need to be considered	80.0	86.7	80.0	86.7

Table 3 (continued)

Best practice statement	Agreement (%)			
	Importance (%)	Scientific acceptability (%)	Usability (%)	Feasibility (%)
If a patient is being treated for LPR, then approaches to evaluation and management should take into account factors such as symptom severity and patient-related factors such as age, health status, and co-morbid conditions	86.7	86.7	93.3	100

in combination with a plant-based Mediterranean diet was compared to PPI; both groups showed an improvement in RSI, but they were not significantly different from one another [14].

Based on this emerging evidence for the role of diet and lifestyle in management of reflux complaints and given absence of any harms associated with this approach, this panel recommends that diet and lifestyle modifications be part of any treatment approach for LPR. With that said, the panel did not discuss or come to an agreement on any specific diet due to limited data.

Laryngoscopy

3. *If a patient has LPR symptoms without classic GERD complaints, then work-up should include laryngopharyngoscopy.*
4. *If a patient with suspected or presumed LPR has concomitant voice complaints that do not improve with reflux treatment, then referral for laryngoscopy and/or laryngeal videostroboscopy is indicated.*

Laryngopharyngoscopy, with or without stroboscopy, involves the use of a fiberoptic or distal chip video flexible laryngoscope to visually evaluate the appearance and function of the larynx and pharynx. The ability of laryngopharyngoscopy to diagnose reflux remains subject to debate, but it very clearly can evaluate for non-reflux etiologies that may lead to non-specific laryngopharyngeal complaints such as dysphonia, dysphagia, sore throat, throat clearing, and globus. Because the symptoms of LPR are non-specific, the panel advocates that treatment should not be focused exclusively upon reflux unless there is concomitant patient complaint of GERD; as noted, if a patient has laryngopharyngeal complaints suspicious for reflux without classic GERD complaints of heartburn, regurgitation, and water brash, then laryngopharyngoscopy should be part of the patient's work-up. Similarly, if a patient does have concomitant typical GERD symptoms such that laryngopharyngeal complaints and presumed LPR are treated empirically with anti-reflux medications, laryngopharyngoscopy is recommended if complaints persist.

The evidence for these statements relates to both studies that show a number of non-reflux etiologies that can mimic LPR in presentation, as well as the number of patients who are mistakenly treated for LPR when another etiology for patient complaints might be present. A study by Fritz et al. found that 64% of patients referred to a tertiary academic medical center with a diagnosis of LPR were found to have another diagnosis responsible for their symptoms detected during laryngoscopy with stroboscopy [15]. The most common alternative diagnoses found were muscle tension dysphonia, vocal fold polyp, vocal fold nodules, and sulcus or scar. In rare cases, carcinoma was identified [15]. Other studies have demonstrated the importance of adding stroboscopy to traditional laryngoscopy. Stroboscopy allows practitioners to assess vocal fold vibratory properties in addition to the anatomic changes noted on laryngoscopy. In one retrospective study at tertiary voice center, 85% of patients referred for second opinion with an initial LPR diagnosis were found to have an additional vocal pathology after stroboscopy [16].

Of note, although laryngopharyngoscopy is very useful in identifying non-reflux etiologies that may contribute to the patient's symptoms, the role of laryngopharyngoscopy in establishing a diagnosis of LPR remains subject to debate. It is clear that many individual signs thought to be related to reflux (laryngeal edema or erythema, posterior pharyngeal wall pachydermia, vocal process granuloma) might be present in non-reflux patients [17–21]. In order to improve sensitivity and specificity of laryngopharyngoscopy as a possible diagnostic tool, groups have proposed scoring systems that attempt to codify a number of endoscopy findings. For example, the RFS and reflux sign assessment (RSA) [22, 23] look at a number of different exam findings across a number of anatomic subsites, assign a score for each, and try to systematize a reflux diagnosis. The success of these efforts remains subject to debate, with concerns for inter-rater and intra-rater reliability, correlation of physical findings with patient report of symptoms, and correlation of physical findings with response to treatment [24]. Studies on diagnostic utility of laryngopharyngoscopy are ongoing. Current literature supports laryngopharyngoscopy as a valuable tool in assessing for additional or alternate laryngopharyngeal pathologies that might require further evaluation and treatment.

Proton Pump Inhibitors (PPI) and H2RA Therapy

5. *If a patient with presumed LPR whose symptoms respond to initial acid suppression treatments cannot later be weaned from medication without symptom recurrence, then titrate to lowest dose of PPI or H2 antagonist needed for long-term symptom control or consider other options for long-term reflux control.*
6. *If a patient with presumed or demonstrated LPR is taking PPI with improvement in symptoms, then inform patient of reported risks of long-term PPI use and offer alternative treatments if the patient does not want to be on PPIs long-term.*
7. *If PPIs are chosen for use in LPR treatment, then they should be dosed 30–60 min before meals.*
8. *If a patient is prescribed PPIs for LPR empiric treatment, then risks and benefits of PPI use should be reviewed with the patient carefully prior to use.*

The efficacy of PPI and H2RA in reducing acid production in the stomach is well established [3, 25, 26]. PPI therapy functions by blocking the gastric H,K-ATPase, thereby inhibiting gastric acid secretion and has been the main therapeutic approach employed in treating LPR [27]. In contrast, H2RA function by the binding to the histamine-2 receptor on gastric parietal cells thus reducing acid production and secretion [28]. Correspondingly, the use of these drugs in treating GERD complaints is commonplace [29].

Their use in the management of LPR remains controversial. For H2RA, some studies have shown effectiveness with a fast onset of action, as well as being effective in controlling nighttime breakthrough reflux in GERD when already managed with BID PPI. For patients with presumed LPR on daily PPI, the addition of nighttime H2RA has similarly been shown to be effective in controlling symptoms [30–32].

On the other hand, various studies have shown PPIs to be effective in treating LPR with varying success rates for PPI usage ranging between 18 and 87% [33–35]. Optimal duration of treatment has also been debated, with one study demonstrating improvement of symptoms after 2 months [36]. In contrast, more recent studies suggest 6 months of treatment is needed to achieve maximal symptom improvement [30, 31].

These medications are not without possible risk and side effects. PPIs have been proposed to lead to reduction in bone density, hypomagnesemia, iron and B12 deficiency, *C. difficile* infection, acute and chronic kidney disease, and Alzheimer's disease/dementia. These associations were demonstrated in low-quality observational studies and are not established to be causal and therefore the American Gastroenterology Association 2017 practice update recommended against routine screening of bone mineral density or vitamins/minerals (e.g., creatinine, magnesium, or vitamin B12 levels) [37]. For H2RA, additional concerns exist with repeated use leading to tachyphylaxis or tolerance [38]. Another serious consideration with H2RA use is that ranitidine and nizatidine were removed from the market by the FDA due to concern of contamination with N-nitrosodimethylamine (NDMA)—a human carcinogen [39]. However, subsequent FDA-sponsored studies did not reveal a significant risk from NDMA and they questioned the initial concerns raised about the use of ranitidine [40, 41].

In sum, the varying opinions on the relationship between acid reflux and non-specific complaints of dysphonia, dysphagia, throat clearing, and globus are not always well established, and confounding issues such as allergy, dryness, vocal fold paresis, glottic insufficiency, habituated behavioral cough, functional or disorders of pharyngeal-brain interaction, etc. have made it more difficult to establish the benefit of anti-secretory agents in treatment of presumed LPR. At the same time, concerns for potential medication side effects and cost have been increasing. Taken together, these trends drive the current panelists' recommendations that these medications should be used with awareness of risks/benefits, used in a way to maximize pharmacologic effectiveness, and titrated to the lowest dose necessary for symptom control as possible.

Endoscopic Treatment and Surgery

9. *If a patient is being considered for endoscopic or surgical reflux treatment, then a thorough pre-procedure evaluation should be performed to assess esophageal function as part of treatment planning.*
10. *If a surgeon is considering fundoplication for a patient with LPR symptoms in the absence of GERD, then otolaryngologic evaluation is warranted prior to any surgery in order to assess for non-reflux etiologies contributing to patient symptoms.*
11. *If a patient is being considered for endoscopic treatment of LPR, then they should be counseled that its efficacy in LPR patients is not completely understood.*
12. *If a patient with LPR demonstrates good symptom control with medications, then with supportive objective reflux and motility testing, a surgical anti-reflux procedure may be considered as an alternative to continued medication.*

Anti-reflux surgical or endoscopic procedures represent long-term alternatives for confirmed GERD patients (e.g., pH monitoring off acid suppression) who do not wish to be dependent on medication [42]. These procedures function as a barrier therapy focusing on augmentation or tightening of the lower esophageal sphincter—preventing reflux at its source. Laparoscopic or open Nissen fundoplication are surgical procedures through which the gastric

fundus is wrapped 360° around the lower esophageal sphincter (LES), tightening it to prevent reflux. Various other forms of this procedure exist such as the Toupet or Dor fundoplication, in which a partial fundoplication is performed, and the gastric fundus is wrapped to lesser degrees. Further, there have been growing data on the impact of upper esophageal sphincter (UES) incompetence leading to pharyngeal reflux and external augmentation as a means of treatment. Shaker et al. demonstrated in a small case–control study by increasing intraluminal UES pressure through external cricoid pressure, pharyngeal reflux was augmented [43]. In a two-phase prospective clinical trial among a slightly large patient population, Yadlapati et al. further measured the use of an external UES compression device (The Reflux Band) in its effect on reducing pharyngeal reflux events. Authors demonstrated additional improvement in reflux following the addition of the device to PPI therapy [44]. Whereas the rise in data highlights the possible clinical utility of external UES pressure, to date, this has not entered standard practice.

Esophageal testing prior to anti-reflux surgery (1) evaluates the luminal anatomy and rules out malignancy or structural pathology (e.g., barium esophagram), (2) assesses the mucosa for Barrett's esophagus (e.g., upper endoscopy), and (3) confirms the lack of achalasia or major esophageal motility disorders (e.g., high-resolution esophageal manometry) [45]. For example, high-resolution esophageal manometry (HRM) measures peristaltic function of the esophageal body, while the catheter is inserted. When function is impaired, the esophageal body lacks the muscle reserve to overcome the effects of an anti-reflux fundoplication wrap. As a result, patients can experience post-operative dysphagia [46]. In disorders such as achalasia, where peristalsis is completely absent or impaired, fundoplication is therefore an absolute contraindication. In milder disorders affecting esophageal motility, such as ineffective esophageal motility (IEM), surgeons are often faced with a challenge on how best to proceed—particularly given the common association of GERD with IEM. In this minor motility disorder, > 70% of peristaltic waves are ineffective and patients are at a higher risk of developing post-operative dysphagia following a Nissen fundoplication [47]. In this case, a partial fundoplication may be the preferred procedure, although robust evidence is lacking and the optimal anti-reflux surgical approach among patients with evidence of IEM remains debated [48]. In recognition of the potential side effects following anti-reflux surgery, the expert panel agreed upon the importance of assessing esophageal function prior to reflux treatment. By doing so, surgeons may tailor the endoscopic or surgical anti-reflux procedure to best fit the needs of the patient.

Fundoplication is an effective treatment for GERD [49]. The role of fundoplication in LPR, in contrast, is still emerging, though some literature suggests that it can be effective as well. For instance, limited retrospective studies have demonstrated Nissen fundoplication to be efficacious among LPR patients and those suffering with chronic cough who were diagnosed using hypopharyngeal–esophageal multichannel intraluminal pH with dual pH catheter testing (HEMII-pH) [50, 51]. In patients with positive pharyngeal events on pH-impedance testing for LPR, and when compared to PPI treatment, fundoplication was associated with better long-term symptom control giving rise to recommendations that patients should be counseled that efficacy of these procedures for LPR is not yet fully elucidated and success is far from guaranteed [52].

Philosophy and Empiric Therapy

13. *If a patient with presumed LPR responds to initial treatment but has persistent complaints even when titration/addition of medication has reached a plateau, then objective testing such as pH-impedance reflux testing can be pursued to help identify refractory reflux or suggest, if reflux is adequately controlled, that non-reflux etiologies for patient complaints need to be considered.*
14. *If a patient with presumed LPR has reached therapeutic plateau with reflux treatment and still has persistent symptoms, then consider evaluation of non-reflux etiologies for common complaints such as globus pharyngeus, cough, throat clearing, hoarseness,* etc. *that had previously been attributed to LPR.*
15. *If a patient is sent for objective reflux testing, then the referring physician should think critically about testing on therapy vs off therapy relative to interpretation of results.*
16. *If a patient with suspected LPR does not have any response to an adequate empiric trial of antacid medication, then objective testing such as pH-impedance and high-resolution esophageal manometry testing can be pursued to help identify refractory non-acidic or weakly acidic reflux or to suggest that etiologies other than reflux for patient complaints need to be considered.*
17. *If a patient is being treated for LPR, then approaches to evaluation and management should take into account factors such as symptom severity and patient-related factors such as age, health status, and co-morbid conditions.*

These recommendations about overall approaches to LPR support an awareness on the part of panelists that not every patient experiences LPR similarly—based on patient-centered principles of maximizing potential treatment benefit and minimizing treatment risk, approaches to LPR treatment need to account for factors such as

certainty of reflux diagnosis and severity of symptoms. These principles underlie prior recommendations regarding diet and lifestyle modifications, medication titration, the role of endoscopy in assessing for non-reflux etiologies of laryngopharyngeal complaints, and the role of surgery in controlling reflux. A holistic view of the recommendations listed in this section and others emphasizes that while LPR is a prevalent cause of laryngopharyngeal complaints, it is not the only cause of non-specific laryngopharyngeal complaints such as dysphonia, dysphagia, throat clearing, and globus pharyngeus. Therefore, objective testing can provide guidance, particularly when performing off therapy to confirm or exclude reflux. It is also important to recognize limitations of testing. Given HRM is a static measurement of time (e.g., approximately 25–30 min), esophageal dysmotility disorders in theory may occur outside this window. However, this limitation is thought to be more relevant in spastic disorders. Further pH impedance is a measurement of a 24-h period. It is well recognized that patients can experience day-to-day variability of reflux, and therefore, acidic reflux events occurring more frequently outside of this window theoretically can be missed.

While an escalating degree of reflux care is certainly appropriate for patients in whom reflux has been demonstrated, reflux treatment for those with suspected or presumed reflux needs to be more circumspect; in patients for whom laryngopharyngeal complaints do not respond or only partially respond to reflux treatment, other etiologies for patient complaints should be investigated, presence/absence and degree of refractory reflux investigated by objective testing, and a personalized plan-of-care designed [33, 53, 54]. An increasing number of studies are utilizing approaches which follow these general principles designed to individualize and optimize care. For instance, empiric therapy algorithms have been devised to minimize PPI dosing and prioritize upfront objective testing. Additionally, various studies have described algorithms for LPR patients that fail PPI treatment. In one recent study, patients underwent pH-impedance and high-resolution manometry testing and were categorized as either non-acid reflux patients, breakthrough-acid reflux patients, or non-reflux patients. Non-acid reflux patients and breakthrough patients were considered for esophagoscopy as well as surgical barrier therapy, whereas non-reflux patients had alternative etiologies investigated. This approach has not only been shown to be clinically useful, but may be cost effective [3].

Discussion

In recent years, there have been advances in the treatment of LPR, including evolutions in medical therapies, changing indications for procedural interventions, and the role of lifestyle modifications. In this study, using the modified four-round Delphi method, a multidisciplinary expert panel of 15 members developed a list of 17 consensus statements for the treatment of LPR supported by agreement on the importance, scientific acceptability, usability, and feasibility of each statement. The primary target users of these consensus statements include all medical providers at all levels of health care, ranging from tertiary care hospitals to community practices. This consensus statement on the treatment of LPR should serve as guidance for everyday clinical management, filling a gap that remains in clinical practice.

When it came to medical considerations, proposed statements focused on treatment with lifestyle modifications, PPI therapy, alginates, and H2RA. Management with H2RA and PPI have been the mainstay of LPR treatment for many years [27], with well-developed literature reviewing potential indications for their use, their potential efficacy, and potential pitfalls in their use as they relate to the uncertainty of the LPR diagnosis, cost, side effects, and dosing schedules which do not maximize the biopharmacologic effect of these medications. Given how common these medications have become in clinical practice it is not surprising that the panel was able to reach agreement on multiple statements designed to improve the clinical effectiveness and "best practice" use of PPI and H2RA for LPR.

In contrast, alginates are a treatment approach of LPR about which less is known. Despite emerging evidence as to its overall efficacy and use by members of the expert panel, the paucity of existing literature may have driven disagreement among the panel concerning alginate use. Though alginate statements had been proposed, none reached the $\geq 80\%$ agreement (score 7–9) threshold for all four criteria and none are included in this consensus document. This may reflect that studies on the roles of alginates in the treatment of LPR remain scarce and limited. Despite evidence suggesting that the alginate raft is intended to physically limit reflux of gastric contents proximally and that alginates can potentially be an effective barrier agent in LPR of any pH [33, 55], more literature is likely needed to establish its clinical value.

Similarly, the panel was able to reach consensus on statements regarding surgical fundoplication, but not on transoral incisionless fundoplication (TIF)—perhaps for the same reason. While there is a literature on the role of Nissen fundoplication in treatment of LPR [50, 52, 56],

TIF is a relatively new procedure. It is an endoscopically performed 270° wrap for patients with less than 3 cm hiatal hernias. Two retrospective studies have reported improved LPR symptoms and ability to discontinue PPIs following TIF [57, 58]. The most recent study evaluating TIF and LPR demonstrated high rates of normalization of RSI, acid exposure time, and discontinuation of PPI usage [59]. Further data are needed, especially long-term studies, demonstrating clinical durability of TIF intervention in LPR patients.

These examples about alginates as compared to PPI and TIF as compared to fundoplication are chosen to illustrate the way in which treatment paradigms for reflux are constantly evolving. These examples also highlight the ways in which the modified Delphi consensus methodology, by design, favored statements for which the importance, scientific acceptability, usability, and feasibility could be agreed upon—leading to a collection of statements concerning LPR treatment that the panelists truly consider current best practices. In an atmosphere where concerns persist regarding overdiagnosis of LPR, burdensome healthcare costs due to LPR, potential side effects of popular LPR medications, and poor efficacy of empiric reflux medication trials for suspected LPR as compared to placebo, there is need for consensus statements such as these to help guide therapy.

Currently, we are limited by evidence-based recommendations for practitioners to manage patients symptoms, particularly among practitioners who do not have convenient access to pH or pH-impedance probe testing (off PPI therapy), yet remained faced with treating patients presenting with very common complaints such as throat irritation and globus. This is relevant as prior society guidelines have recommended against empiric treatment of LPR with PPI therapy, with typical GERD symptoms are absent [60]. Recently, the American College of Gastroenterology [29] updated its prior guidelines on reflux, to offer more expansive guidance concerning extra-esophageal manifestations of GERD. These updated guidelines are similar to the recommendations in this manuscript regarding statements that non-GERD etiology for laryngopharyngeal patient complaints should be evaluated and that escalating levels of reflux care be reserved for patients with GERD and/or objective evidence of reflux. But given these guidelines were focused in GERD, a literature gap remained on how to manage patients with LPR. In contrast to the prior guidelines, the current consensus statements supported in this manuscript are multidisciplinary, focus on LPR rather than GERD, focus on treatment rather than diagnosis, and are based on consensus voting and discussion (incorporating scientific validity alongside other constructs such as importance, usability, and feasibility) rather than literature review alone by very small group of experts.

The current study is not without limitations. The expert panel includes a mixture of otolaryngologists, gastroenterologists, and general surgeons, given these are the primary providers diagnosing and managing patients with LPR. This team, though unbalanced in the proportion of experts from each specialty, is thought to mimic national practice patterns in management of laryngopharyngeal complaints. However, we also recognize the uneven distribution of specialists may possibly introduce bias in the consensus statements. Otolaryngologists, and more specifically fellowship trained laryngologists, were chosen for their practice focus of exclusively evaluating and managing laryngopharyngeal complaints; gastroenterologists were included due to their practice emphasis on the evaluation and management of both LPR and GERD; general surgeons were chosen for their focus on anti-reflux surgeries. Furthermore, the methodology applied to this study used a modified Delphi method among experts to reach consensus by rating each statement on the basis of importance, scientific acceptability, usability, and feasibility. These ratings were the perspective of individual experts and thus, by definition, the resulting consensus statements reflect subjective opinion, although each voting panelist was asked to consider the evidence-base for each statement as they voted. Additionally, the involved experts all participate in clinical practice and scientific research on reflux, which provides valuable insight and perspective into the development of the presented consensus statements.

In conclusion, 15 recognized experts, in the fields of gastroenterology, otolaryngology, and general surgery from three countries around the world, took part in developing consensus statements on LPR treatment. Experts participated in a four-round modified Delphi process concerning various perspectives on the treatment of LPR, focusing on the four categories of importance, scientific acceptability, usability and feasibility. The consensus statements of this paper will hopefully provide more clarity and guidance on the current treatment considerations for LPR and guide future areas of research.

Declarations

Competing interest AK, SD, JL, JA, JB, MF, MM, GP and LA—None. JB—Consultant for Diversatek Healthcare and Merck. JC—Consultant: Alnylam, Isothrive, Medtronic, Phathom, Pfizer, Regeneron, Sanofi. PB—Co-founder Reflux Gourmet, LLC. WC—Advisory Board for Ironwood, Takeda, and Phathom Pharmaceuticals. RF—Advisor for Takeda, Daewoong, Medtronic, Phathom pharmaceuticals, Neurogastrx, GERDCare, Celexio; Speaker for Astrazeneca, Takeda, GI Supply, Eisai, Johnson & Johnson. AO—Consultant for GI Supply & Laborie Medical Inc. ES—Speaker for Abbvie, AGPharma, Alfasigma, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Innovamedica, Malesci, Novartis, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Unifarco; consultant for Alfasigma, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Falk, Fresenius Kabi, Janssen, Merck

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