Diagnostic Testing for Laryngopharyngeal Reflux Disease

The Role of 24-hour Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance-pH Monitoring

Jennifer Aoun, MD[a,*], Vinciane Muls, MD[a], Pierre Eisendrath, MD, PhD[a], Jérôme R. Lechien, MD, PhD, MS[b]

KEYWORDS

• Laryngopharyngeal reflux disease • Diagnostic modalities • HEMII-pH • Impedance

KEY POINTS

- Laryngopharyngeal reflux disease (LPRD) presents with a wide range of nonspecific signs and symptoms, making it challenging to diagnose based solely on clinical findings.
- Objective diagnostic tools are necessary to differentiate LPRD from other conditions with similar presentations.
- Hypopharyngeal-esophageal intraluminal impedance with pH monitoring (HEMII-pH) is the current gold standard in diagnosing LPRD, as it identifies acidic, weakly acidic, and nonacidic liquid, mixed, or gaseous esophageal full column and pharyngeal reflux events.
- The widespread use of HEMII-pH as a first-line diagnostic tool remains limited by its availability, cost, and time-consuming interpretation.

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 morphologic and/or neurologic changes in the upper aerodigestive

[a] Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, CHU Saint-Pierre, Brussels, Belgium; [b] Department of Otorhinolaryngology and Head and Neck Surgery, CHU Saint-Pierre, Brussels, Belgium
* Corresponding author. Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Université Libre de Bruxelles (ULB), Rue Haute 322, 1000 Brussels, Belgium.
E-mail address: jennifer.aoun@stpierre-bru.be

Otolaryngol Clin N Am 58 (2025) 441–449
https://doi.org/10.1016/j.otc.2024.12.001 **oto.theclinics.com**

Abbreviations	
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
HEMII-pH	hypopharyngeal-esophageal multichannel intraluminal impedance and pH monitoring
LPR	laryngopharyngeal reflux
LPRD	laryngopharyngeal reflux disease
MII	multichannel intraluminal impedance
MII-pH	multichannel intraluminal impedance-pH monitoring
PPI	proton pump inhibitor
PRE	pharyngeal reflux event
PRO	patient-reported outcomes
RSI	Reflux Symptom Index
RSS	Reflux Symptom Score
RSS-12	Reflux Symptom Score short version
SAP	Symptom Association Probability
SI	Symptom Index

tract.[1] As LPRD slowly gained popularity in Western countries in the past few decades, particularly in the otolaryngology field, its diagnosis remained challenging. Unlike gastroesophageal reflux disease (GERD), LPRD is associated with a spectrum of nonspecific signs and symptoms, many of which overlap with other common ear, nose, and throat conditions, complicating the clinical diagnosis.[2] In an effort to address the current challenges in LPRD diagnosis, the 2024 IFOS-Dubai Consensus highlights the need to complement the diagnostic evaluation with more objective tools.[3] The 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance and pH monitoring (HEMII-pH) has emerged as a reliable technique to objectify the presence of LPRD. The IFOS-Dubai consensus experts supported LPRD diagnosis when more than 1 pharyngeal reflux event (PRE) has been captured at the 24-hour HEMII-pH monitoring.[3] Given the importance of HEMII-pH in LPRD diagnosis and management, the aim of article is to explore the role and features of HEMII-pH in diagnosing LPRD.

HISTORY OF DIAGNOSTIC TOOLS FOR LARYNGOPHARYNGEAL REFLUX DISEASE

Since the first publication demonstrating the differences between GERD and LPRD,[4] multiple diagnostic approaches have been proposed, associating validated patient-reported outcomes (PRO) questionnaires, endoscopic findings, empirical proton pump inhibitor (PPI) therapy trials, salivary pepsin measurements, oropharyngeal pH studies, and pH-impedance monitoring.[3]

Objective Approaches

Among objective approaches, the single-probe esophageal pH study was rapidly replaced by the dual or triple-probe pH monitoring, found to be more appropriate for detecting acidic PREs.[5] However, pH-testing devices without impedance sensors failed to detect non-acid PREs, and consequently, did not diagnose patients with weakly acidic or alkaline reflux disease. The use of pharyngeal sensors instead of proximal esophageal sensors was strengthened by Kawamura and colleagues, who observed that less than half of the distal-to-proximal esophageal reflux events reach the pharynx.[6] This observation is most likely explained by the protective contraction of the upper esophageal sphincter, filtering some proximal esophageal reflux episodes and preventing the retrograde backflow from reaching the pharynx.[7]

The development of the impedance technology and the growing adoption of impedance-pH monitoring devices in academic centers of Western countries[8,9] have led to an evolution in the objective testing approach for LPRD in the twenty-first century. Thus, authors began to increasingly use esophageal multichannel intraluminal impedance-pH monitoring (MII-pH) for the diagnosis of LPRD, as well as HEMII-pH monitoring over the past few years.[10,11] To date, HEMII-pH is considered the gold standard diagnostic tool for LPRD diagnosis, owing to its ability to document full column esophageal and esophago-pharyngeal reflux events.[3]

Clinical Approaches

The limited availability and high cost of impedance-pH testing have led some authors to propose alternative diagnostic approaches for LPRD.[12,13] Thus, for the past 2 decades, validated PRO questionnaires such as Reflux Symptom Score (RSS),[14] the short version (RSS-12)[15] and the Reflux Symptom Index (RSI)[12] were developed and validated in several languages.[16–20] In their respective validations, authors calculated diagnostic thresholds associated with high sensitivities and better correlation with objective findings. These clinical scores were used for LPRD diagnosis and for monitoring of symptoms throughout a therapeutic course. Similarly, laryngoscopic findings scores were developed to support LPRD diagnosis, but sign instruments are subject to high interobserver variability and therefore are insufficient to confirm the diagnosis.[21]

The most widely used approach for LPRD diagnosis remains the prescription of an empirical therapeutic trial and the documentation of symptoms relief.[5,22] In fact, PPIs have been used empirically to treat patients with suspected LPRD based on clinical evaluation, retrospectively suggesting LPRD diagnosis in responders. However, this approach's main limitation is the lack of consensus about the definition of an adequate therapeutic response. Moreover, nonresponders may have alkaline or weakly acidic reflux, requiring alginate therapy and not PPIs for symptomatic control. Consequently, these patients might be falsely categorized as patients with refractory symptoms, while they should respond to alginate or antacids. Indeed, few PREs are acidic.[11] Moreover, a systematic review and meta-analysis evaluating PPIs versus placebo failed to show superiority of PPIs in the empiric management of LPRD.[23] Finally, patients may have other underlying pathologies responsible for LPRD-like symptoms such as allergy or chronic cough, making the clinical diagnosis and follow-up challenging without objective testing.

Experimental or Unvalidated Approaches

Salivary pepsin measurements

Salivary pepsin measurements have emerged as a noninvasive sensitive tool for diagnosing LPRD. Pepsin is a gastric enzyme, whose presence in the upper digestive tract and particularly in the laryngopharyngeal area can be interpreted as direct evidence of reflux.[24] Ongoing research is being conducted to determine adequate times of salivary sample collection and the number of samples needed and the cut-off pepsin concentration for LPRD diagnosis. Recent studies supported the cut-off of at least 16 ng/mL on fasting and bedtime salivary samples as being associated with the highest detection rate for LPR.[25,26] However, pepsin cannot be detected in up to one-third of patients, leading many practitioners to view this approach as nonvalidated.[25,26]

Oropharyngeal pH monitoring

Although it seems like a promising technique for the detection of PREs, oropharyngeal pH monitoring has significant limitations and consequently failed to become the gold

standard diagnostic test for LPRD. Although it can effectively detect acidic and weakly acidic reflux episodes, the lack of international consensus on diagnostic criteria and the absence of esophageal sensors makes it less reliable compared with other techniques, such as HEMII-pH.[27] Given the lack of HEMII-pH device with nasopharyngeal sensor, oropharyngeal pH monitoring should be interesting for documenting potential nasopharyngeal reflux events in sinonasal or otitis media disorders associated with reflux.[3] Future studies are needed to confirm this point.

THE HYPOPHARYNGEAL-ESOPHAGEAL MULTICHANNEL INTRALUMINAL IMPEDANCE-pH MONITORING

The 24-hour HEMII-pH is a recent diagnostic technique that combines the advantages of pH monitoring with a multichannel intraluminal impedance (MII), providing an objective identification of PREs. This technique detects acidic, weakly acidic, and nonacidic reflux events, and provides information on the time of reflux episodes (daytime, nighttime), positions associated with the reflux events (upright, supine) and the composition of the refluxate (gaseous, liquid, mixed), providing a comprehensive analysis of reflux patterns in LPRD patients.[11]

Placement of Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance-pH Monitoring

The HEMII-pH probe is usually composed of 6 impedance channels along with 2 pH electrodes. At least 2 impedance channels are to be placed within the proximal esophagus and 1 impedance channel in the hypopharyngeal area, above the upper esophageal sphincter. After insertion of the probe transnasally, the distal pH sensor is positioned 5 cm above the lower esophageal sphincter, while the proximal pharyngeal pH sensor is placed 1 cm above the upper esophageal sphincter. The sensors positions can be controlled by chest radiography, nasofibroscopy, pH variation measurements, or the concomitant use of esophageal manometry.[28]

Features of the Reflux Disease at Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance-pH Monitoring

For a long time, LRPD was considered as an extraesophageal manifestation of GERD. In 1991, following dual-probe pH monitoring studies, LPRD or occult GERD was described as being weakly acidic or alkaline, and occurring in upright positions, mainly during daytime.[4] These characteristics in addition to the predominant gaseous nature of the PREs, and their occurrence outside the 1-hour postmeal interval, were later confirmed by Lechien and colleagues using the 24-hour HEMII-pH monitoring.[11] Conversely, GERD's profile at the HEMII-pH monitoring seems different. It is characterized by a liquid composition, favored in the supine position, and almost always acidic.[28] Interestingly, the prevalence of concomitant GERD among LPR patients is high, reaching almost 50% in patients with laryngopharyngeal symptoms.[29] It would be reasonable to consider GERD as a risk factor for LPRD, and a potential predictor for acidic LPRD.[29] Nonetheless, the difference in the pathophysiological mechanisms and the clinical manifestations between LRPD and GERD strengthens the need to diagnose and treat these 2 entities as separate diseases.

Interpretation of a Pharyngeal Reflux Episode on Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance-pH Monitoring

Fig. 1 shows a PRE recorded on HEMII-pH tracing. The typical tracing usually demonstrates esophageal and pharyngeal pH recordings together with the multilevel

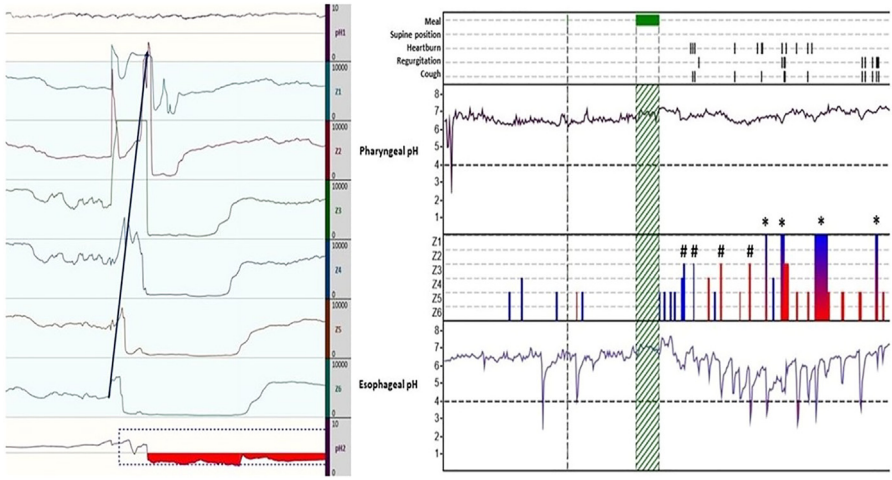

Fig. 1. Illustration of a comprehensive overview obtained through HEMII-pH monitoring.

esophageal and pharyngeal impedance measurements. As seen in **Fig. 1**, a liquid PRE is defined as an upward migration of a 50% drop in the baseline impedance, recorded on all impedance sensors, starting from the distal esophagus (Z6) reaching the proximal esophagus (Z3) and ultimately the pharyngeal sensor (Z1). This change in impedance is accompanied at the level of the pharyngeal sensors by pH fluctuations if the refluxate is acidic (pH<4) or weakly acidic ($4 \geq$ pH ≤ 7) such as the presented case, or no changes in the pharyngeal pH in case of an alkaline PRE (pH >7). A PRE (*) is demonstrated as an impedance variation bar reaching the pharyngeal impedance sensor (Z1), whereas a full-column esophageal reflux event (#) is shown as an impedance variation bar reaching the proximal esophageal sensor (Z3). Symptoms correlation is crucial in the analysis of HEMII-pH tracings. This is performed by calculating the Symptom Index (SI) and the Symptom Association Probability (SAP), irrespective of the esophageal pH variations.

Clinical Relevance and Implications

In contemporary diagnostic algorithms for LPRD, clinicians are advised to refer to the 24-hour HEMII-pH monitoring when available, before starting empiric pharmacotherapy, to confirm LPRD and tailor treatment propositions accordingly.[30] As previously discussed, the nonspecificity of the symptoms and signs of LRPD advocates for the use of more objective methods to confirm the diagnosis. To date, HEMII-pH monitoring is considered the most reliable diagnostic method for objectification of PREs.

The use of 24-hour HEMII-pH monitoring has significant clinical implications in our practice. This technique provides objective measures of PREs supporting the diagnosis of LPRD, minimizing the confusion with other conditions with similar clinical presentations. Furthermore, by identifying the characteristics of the reflux events, such as the nature, the timing, and the pH, HEMII-pH helps clinicians tailor treatment strategies according to the patients' profiles, such as alginate-based therapies, dietary modifications, or PPI when needed.[31] More than 50% of LPRD do not require long-term treatment.[32] Finally, HEMII-pH monitoring can be a valuable tool in research settings, providing objective data on esophageal and paraesophageal reflux events,

correlating them with symptoms and laryngeal findings. This can help further refine the existing diagnostic criteria for LPRD, and evaluate long-term outcomes of LRPD patients. Therefore, it is reasonable to conclude that HEMII-pH provides valuable answers for patients facing unclear diagnoses and health care odyssey driven by the lack of awareness about LPRD, ultimately helping to reduce health care system costs.[33,34]

Comparison with Other Traditional Diagnostic Modalities

HEMII-pH provides several advantages over traditional pH monitoring techniques. Indeed, the combination of pH and impedance measures allows the detection of full column gastro-eso-pharyngeal reflux events independently of the pH, making it particularly useful in identifying nonacidic and gaseous PREs, known to be predominant in LPRD.[11] Moreover, HEMII-pH captures both pharyngeal and proximal esophageal reflux episodes, distinguishing LPR from proximal gastroesophageal reflux (GER), making it more reliable than MII-pH without pharyngeal sensors, for LPRD diagnosis.[3] Furthermore, when compared with oropharyngeal pH monitoring (Restech Dx), HEMII-pH detected more acidic events (pH<4), while oropharyngeal pH monitoring recorded a higher total number of events and longer event durations.[35] This suggests different sensitivities for both techniques in the detection of LPR.

Limitations of Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance and pH Monitoring

Despite its advantages, HEMII-pH is far from being perfect. First, the procedure requiring the placement of a catheter is considered invasive and uncomfortable for some patients, notably those with esophageal or laryngopharyngeal mucosa hypersensitivity.[36] Other limitations include its elevated cost and limited availability in many countries. Furthermore, PREs may occur outside the 24-hour monitoring period, resulting in false negative analysis. Despite these limitations, the overall advantages of HEMII-pH in diagnosing LPRD make it a valuable tool to use in clinical practice.

FUTURE DIRECTIONS AND PERSPECTIVES

Looking toward future advancements, a prolonged recording using 48-hour or 72-hour HEMII-pH monitoring could be pivotal in assessing the day-to-day variability of reflux patterns, increasing the diagnostic yield for intermittent reflux episodes missed during the 24-hour study. In addition, the development of devices integrating pH-impedance monitoring with enzyme detection such as pepsin or bile salts could lead to new diagnostic possibilities for LPRD. Enzymatic profiles found in the saliva or pharyngeal secretions of patients could serve as a biomarker, correlating PREs with LPRD symptoms. Finally, extending pH impedance sensors into the nasopharynx could be an important step in evaluating nasopharyngeal reflux, potentially involved in several diseases associated with a significant cost burden (recalcitrant rhino-sinusitis and otitis media with suppuration, among others).[37,38] Indeed, studies have shown increased nasal pepsin concentration in patients with LPRD compared with healthy individuals.[39,40]

SUMMARY

LPRD diagnosis remains challenging given the variable clinical presentation and nonspecific signs and symptoms. Validated PRO questionnaires, nasofibroscopic signs, and pH-impedance monitoring contribute to the diagnostic process, each presenting limitations when used alone. Among the available techniques, 24-hour HEMII-

pH monitoring offers the most comprehensive approach for LPRD diagnosis and management by identifying the different PRE profiles, allowing correlation with the patients' symptoms, permitting tailored treatment propositions, limiting extensive diagnostic journeys, and reducing health care costs. However, HEMII-pH has its own limitations. Moving forward, further research is needed for the development of more precise diagnostic criteria for the available existing tools, in order to improve the accuracy and consistency of LPRD diagnosis.

CLINICS CARE POINTS

- Clinicians should consider 24-hour HEMII-pH monitoring as a diagnostic tool to confirm LPRD in patients with extra-esophageal reflux symptoms, particularly when traditional diagnostic methods such as endoscopy or esophageal pH-impedance testing are inconclusive.
- HEMII-pH objectively measures the pH of reflux episodes while simultaneously correlating them with patients' reported symptoms, minimizing over-diagnosis and avoiding unnecessary treatment, particularly the over-prescription of proton pump inhibitors (PPIs).
- Data from HEMII-pH monitoring enables tailored patient counseling on targeted strategies to minimize symptoms triggers, such as meal timing, portion sizes and posture-related behaviors.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Lien H-C, Lee P-H, Wang C-C. Diagnosis of laryngopharyngeal reflux: past, present, and future—a mini-review. Diagnostics 2023;13(9):1643.
2. Salgado S, Borges LF, Cai JX, et al. Symptoms classically attributed to laryngopharyngeal reflux correlate poorly with pharyngeal reflux events on multichannel intraluminal impedance testing. Dis Esophagus 2023;36(1). https://doi.org/10.1093/dote/doac041.
3. Lechien JR, Vaezi MF, Chan WW, et al. The Dubai definition and diagnostic criteria of laryngopharyngeal reflux: the IFOS consensus. Laryngoscope 2024;134(4):1614–24.
4. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991;101(4 Pt 2 Suppl 53):1–78.
5. Ford CN. Evaluation and management of laryngopharyngeal reflux. JAMA 2005;294(12):1534–40.
6. Kawamura O, Aslam M, Rittmann T, et al. Physical and pH properties of gastroesophagopharyngeal refluxate: a 24-hour simultaneous ambulatory impedance and pH monitoring study. Am J Gastroenterol 2004;99(6):1000–10.
7. Ulualp SO, Toohill RJ, Hoffmann R, et al. Pharyngeal pH monitoring in patients with posterior laryngitis. Otolaryngol Head Neck Surg 1999;120(5):672–7.
8. Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004;53(7):1024–31.

9. Tutuian R, Vela MF, Shay SS, et al. Multichannel intraluminal impedance in esophageal function testing and gastroesophageal reflux monitoring. J Clin Gastroenterol 2003;37(3):206–15.
10. Hoppo T, Sanz AF, Nason KS, et al. How much pharyngeal exposure is "normal"? Normative data for laryngopharyngeal reflux events using hypopharyngeal multichannel intraluminal impedance (HMII). J Gastrointest Surg 2012;16(1):16–25.
11. Lechien JR, Bobin F, Muls V, et al. Hypopharyngeal-esophageal impedance-pH monitoring profiles of laryngopharyngeal reflux patients. Laryngoscope 2021;131(2):268–76.
12. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002;16(2):274–7.
13. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope 2001;111(8):1313–7.
14. Lechien JR, Bobin F, Muls V, et al. Validity and reliability of the reflux symptom score. Laryngoscope 2020;130(3). https://doi.org/10.1002/lary.28017.
15. Lechien JR, Bobin F, Rodriguez A, et al. Development and validation of the short version of the reflux symptom score: reflux symptom Score-12. Otolaryngol Head Neck Surg 2021;164(1):166–74.
16. Guimarães I, Batista AP, Quintal A, et al. The reflux symptom score-12: cross-cultural adaptation and validation for European Portuguese speakers with laryngopharyngeal reflux. J Voice 2023. https://doi.org/10.1016/j.jvoice.2023.06.016.
17. Almothahbi AS, Alasqah MI, Mesallem T, et al. Translation and validation of the Arabic version of the reflux symptom score, short version 12 (RSS-12). J Voice 2023. https://doi.org/10.1016/j.jvoice.2023.05.011.
18. Min HK, Jeon SY, Lechien JR, et al. Translation and validation of the Korean version of the reflux symptom score. J Voice 2024;38(2):545.e1–8.
19. Arslanoğlu A, Durgut O. Linguistic adaptation, reliability, and validation of the Turkish version of the reflux symptom index. J Voice 2022;36(1):146.e1–4.
20. Calvo-Henríquez C, Ruano-Ravina A, Vaamonde P, et al. Translation and validation of the reflux symptom index to Spanish. J Voice 2019;33(5):807.e1–5.
21. Patel DA, Blanco M, Vaezi MF. Laryngopharyngeal reflux and functional laryngeal disorder: perspective and common practice of the general gastroenterologist. Gastroenterol Hepatol 2018;14(9):512–20.
22. Lechien JR, Akst LM, Hamdan AL, et al. Evaluation and management of laryngopharyngeal reflux disease: state of the art review. Otolaryngol Head Neck Surg 2019;160(5):762–82.
23. Lechien JR, Saussez S, Schindler A, et al. Clinical outcomes of laryngopharyngeal reflux treatment: a systematic review and meta-analysis. Laryngoscope 2019;129(5):1174–87.
24. Barona-Lleó L, Duval C, Barona-de Guzmán R. Salivary pepsin test: useful and simple tool for the laryngopharyngeal reflux diagnosis. Acta Otorrinolaringol Esp 2018;69(2):80–5.
25. Zeleník K, Hránková V, Vrtková A, et al. Diagnostic value of the Peptest™ in detecting laryngopharyngeal reflux. J Clin Med 2021;10(13):2996.
26. Lechien JR, Bobin F. Diagnostic value of fasting and bedtime saliva pepsin measurements in laryngopharyngeal reflux. Biomedicines 2024;12(2):398.
27. Lechien JR, Chan WW, Akst LM, et al. Normative ambulatory reflux monitoring metrics for laryngopharyngeal reflux: a systematic review of 720 healthy individuals. Otolaryngol Head Neck Surg 2022;166(5):802–19.
28. Lechien JR. Clinical update findings about pH-impedance monitoring features in laryngopharyngeal reflux patients. J Clin Med 2022;11(11):3158.

29. Lechien JR, Bobin F, Muls V, et al. Gastroesophageal reflux in laryngopharyngeal reflux patients: clinical features and therapeutic response. Laryngoscope 2020; 130(8). https://doi.org/10.1002/lary.28482.
30. Krause AJ, Walsh EH, Weissbrod PA, et al. An update on current treatment strategies for laryngopharyngeal reflux symptoms. Ann N Y Acad Sci 2022; 1510(1):5–17.
31. Lechien JR. Personalized treatments based on laryngopharyngeal reflux patient profiles: a narrative review. J Pers Med 2023;13(11):1567.
32. Lechien JR, Lisan Q, Eckley CA, et al. Acute, recurrent, and chronic laryngopharyngeal reflux: the IFOS classification. Laryngoscope 2023;133(5):1073–80.
33. Lechien JR, Mouawad F, Mortuaire G, et al. Awareness of European otolaryngologists and general practitioners toward laryngopharyngeal reflux. Ann Otol Rhinol Laryngol 2019;128(11):1030–40.
34. Lechien JR, Leclercq P, Brauner J, et al. Cost burden for healthcare and patients related to the unawareness towards laryngopharyngeal reflux. Eur Arch Oto-Rhino-Laryngol 2024. https://doi.org/10.1007/s00405-024-08881-w.
35. Vance D, Park J, Alnouri G, et al. Diagnosing laryngopharyngeal reflux: a comparison between 24-hour pH-impedance testing and pharyngeal probe (Restech) testing, with introduction of the Sataloff score. J Voice 2023;37(5):737–47.
36. Jamieson JR, Stein HJ, DeMeester TR, et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992;87(9):1102–11.
37. Samuels TL, Johnston N. Pepsin in gastroesophageal and extraesophageal reflux: molecular pathophysiology and diagnostic utility. Curr Opin Otolaryngol Head Neck Surg 2020;28(6):401–9.
38. Zeleník K, Javorská Z, Taimrová R, et al. Association between inferior turbinate hypertrophy and extraesophageal reflux. JAMA Otolaryngol Head Neck Surg 2022;148(8):773–8.
39. Ozmen S, Yücel OT, Sinici I, et al. Nasal pepsin assay and pH monitoring in chronic rhinosinusitis. Laryngoscope 2008;118(5):890–4.
40. Lechien JR, Saussez S, Hopkins C. Association between laryngopharyngeal reflux, gastroesophageal reflux and recalcitrant chronic rhinosinusitis: a systematic review. Clin Otolaryngol 2023;48(4):501–14.