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Laryngopharyngeal reflux: a diagnostic and therapeutic challenge for the otolaryngologist and gastroenterologist

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ABSTRACT:

Laryngopharyngeal reflux disease (LPRD) is an entity separate from GERD in which the refluxate (acid, pepsin, bile salts, etc.) crosses the upper esophageal sphincter and irritates the particularly sensitive pharyngeal and laryngeal mucosa, resulting in symptoms such as hoarseness, coughing, and grunting, frequently without the typical heartburn or esophageal erosions. The diagnosis cannot rely solely on the laryngoscopic appearance or the RSI/RFS scales (Reflux Symptom Index/Reflux Finding Score). The reference standard is hypopharyngeal–esophageal multichannel intraluminal impedance with pH monitoring (HEMII-pH), which documents the extent of reflux (acidic, non-acidic, gaseous) reaching the pharynx and allows for LPRD phenotyping and treatment selection. Gastroscopy is reserved mainly for alarm symptoms and complications of GERD. The treatment should be personalized and multidirectional, including lifestyle and diet modification as well as pharmacotherapy targeting the type of reflux. In weak acid/non-acid reflux, an important part is played by alginates (exerting mechanical action within the stomach to reduce postprandial and nocturnal reflux) and topical barrier preparations with hyaluronic acid that form a bioadhesive protective film on the mucosa and promote its regeneration. Prokinetic agents should be considered, especially in patients with motility disorders or distal reflux. Proton pump inhibitors should be used selectively, mainly with documented acid exposure or concomitant typical GERD symptoms. Effective care requires collaboration between an otolaryngologist and a gastroenterologist, with diagnostic and therapeutic decisions being based on the phenotype of reflux as well as the patient's preferences. This personalized approach reduces the risk of over-suppression of gastric acid and increases the clinical response rate.

KEYWORDS: gastroesophageal reflux disease, hyaluronic acid formulations, laryngitis, laryngopharyngeal reflux disease, laryngopharyngeal reflux, prokinetics, reflux

ABBREVIATIONS

AGA – American Gastroenterological Association
CS – chondroitin sulfate
EER – extraesophageal reflux
EGD – esophagoduodenoscopy
GERD – gastroesophageal reflux disease
HA – hyaluronic acid
HEMII-pH – hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring
IFOS – International Federation of ORL Societies
LPR – laryngopharyngeal reflux
LPRD – laryngopharyngeal reflux disease
LPS – laryngopharyngeal symptoms
LVE – laryngovideoendoscopy
MII-pH – multichannel intraluminal impedance-pH monitoring
NBI – Narrow-Band Imaging
PPI – proton pump inhibitor
RFS – reflux finding score
RSA-10 – Reflux Sign Assessment-10
RSI – reflux symptom index
SIBO – small intestinal bacterial overgrowth

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders. It is estimated that more than 13% of the world's adult population experiences GERD symptoms at least once a week. In Poland, according to population-based survey data, as many as 34% of patients presenting to their family physician meet the criteria for the diagnosis or treatment of the disease, regardless of the reason for the presentation. GERD is defined as the retrograde flow of gastric contents into the esophagus that causes bothersome symptoms reducing the quality of life and/or leading to complications. In recent years, numerous guidelines have been published on the diagnosis and treatment of GERD, with an emphasis on therapy personalization and regular assessment of the need for maintenance treatment [1]. Notable publications included the 2022 consensus of the Polish Society of Gastroenterology, the American Gastroenterological Association's (AGA) recommendations update, the second version of the 2023 Lyon Consensus, and the 2024 Guidelines for Family Physicians [1–3].

In 2006, the so-called Montreal definition of the disease distinguished between its esophageal and extraesophageal forms. The latter includes syndromes with a documented causal relationship to reflux, such as the upper airway cough syndrome, the irritable larynx syndrome, reflux-related asthma, and dental erosion. Disease entities with a postulated yet unconfirmed link to reflux, including pharyngitis, sinusitis, idiopathic pulmonary fibrosis, and recurrent otitis media, have also been included in the definition [4]. Extraesophageal reflux (EER) requires collaboration from physicians of various specialties: otolaryngologists, pneumologists, cardiologists, and dentists.

The term laryngopharyngeal reflux (LPR) was introduced by the American Academy of Otolaryngology-Head and Neck Surgery in 2002 [5]. Currently, the form of reflux in which gastric and duodenal contents flow back above the upper esophageal sphincter and reach the throat and larynx to cause morphological and/or neurological changes within the upper gastrointestinal tract, is referred to as the laryngopharyngeal reflux disease (LPRD) [6]. The latest recommendations from the affiliates of the International Federation of ORL Societies (IFOS) point out that GERD and LPRD are now treated as separate disease entities while sharing some of the pathophysiological mechanisms [7]. In LPRD, unlike GERD, the reflux content does not remain long within the esophagus, thus causing no irritation thereof, while irritating the much more sensitive laryngeal mucosa, which is deprived of the protective role of saliva and other defense mechanisms present in the lower esophagus.

Although GERD and LPRD share common pathophysiological mechanisms, they differ in their clinical course and require different diagnostic and therapeutic strategies. GERD remains the primary focus for gastroenterologists, while patients with LPRD symptoms primarily present at otolaryngologists. According to the current guidelines from both gastroenterology and otolaryngology scientific societies, reflux laryngitis cannot be diagnosed solely on the basis of laryngoscopic examination images, which are not specific for reflux. In doubtful or refractory cases, it is recommended that the diagnosis be expanded to include objective methods such as impedance pH-metry and, if necessary, gastroenterologist consultation [1]. Successful diagnosis and treatment of LPRD therefore require a multidisciplinary approach, based on the current recommendations and tailored to the individual patient's needs.

EPIDEMIOLOGY AND ETIOPATHOGENESIS OF LARYNGOPHARYNGEAL REFLUX DISEASE

The first reports from the 1990s were indicative of laryngopharyngeal reflux being present in about 10% of patients consulted by otolaryngologists [8]. A decade later, the prevalence of LPRD symptoms among patients reporting voice disorders was already estimated at 70% [9]. Currently, the reported data vary, with the prevalence of LPRD symptoms being estimated at 1–30% depending on the study population and the diagnostic criteria used [6, 10]. Determining the true incidence of LPRD remains difficult due to the lack of clear diagnostic criteria, as well as to the similarity of LPRD symptoms to those of other disease entities such as chronic sinusitis, allergies, occupational voice diseases, or pharyngitis associated with smoking or alcohol consumption [11].

Contemporary epidemiological data also indicate a significant LPRD-related burden on the health systems. In the US, a patient with chronic laryngeal symptoms undergoes an average of 10 consultations and six diagnostic tests, generating a cost of approx. 5,438 dollars per year, and the total cost of caring for patients with suspected LPRD is estimated at 50 billion dollars per year [12].

The mechanisms of LPRD development are complex and include direct reflux, leading to the contact of gastroduodenal contents (containing hydrochloric acid, pepsin, pancreatic enzymes, bile salts) with the laryngeal mucosa as well as an indirect mechanism,

Tab. I. Differences between laryngopharyngeal symptoms *vs.* laryngopharyngeal reflux *vs.* laryngopharyngeal reflux disease (LPS *vs.* LPR *vs.* LPRD).

NAME	MEANING	DIAGNOSTIC CRITERIA	EXAMPLE
Laryngopharyngeal Symptoms (LPS)	Laryngopharyngeal symptoms (non-specific)	Reported symptoms (hoarseness, globus sensation, grunting, coughing)	Patient: "I constantly experience hoarseness and a scratchy throat"
Laryngopharyngeal Reflux (LPR)	Suspected laryngopharyngeal reflux	Symptoms (LPS) + laryngoscopy image suggestive of reflux	Patient reports symptoms while the physician observes laryngeal irritation and suspects reflux
Laryngopharyngeal Reflux Disease (LPRD)	Laryngopharyngeal reflux disease	Reflux documented in objective studies	The pH-impedance examination shows reflux reaching the larynx

based on the activation of the vagus nerve, which can lead to chronic coughing and increased laryngeal reactivity [11, 13]. The laryngeal mucosa, unlike that lining the esophagus, lacks the squamous epithelium and the buffering effect of saliva, which makes it more susceptible to damage from low pH and digestive enzymes [14, 15]. Reduced salivary volume and pH, as well as lower epidermal growth factor (EGF) levels, were observed in patients with LPRD, impairing epithelial protection and regeneration [16].

Other pathophysiological features of LPRD include the predominance of weak acid or alkaline reflux, the dominance of gaseous reflux experienced in the upright position and during daytime, endocytosis of pepsin within epithelial cells, with pepsin persisting within the cells for more than 36 hours and initiating an inflammatory response [11].

Importantly, even single episodes of reflux beyond the upper esophageal sphincter, especially at pH < 4, can lead to chronic laryngitis and damage that persists for weeks [17]. These changes can be chronic, and their development is facilitated by an imbalance between damaging (acid, enzymes) and protective (saliva, EGF, type III carbonic anhydrase) factors. In addition, studies of refluxate composition confirm that patients with LPRD present with higher levels of pepsin, bile salts, elastase, and trypsin in saliva compared to healthy subjects. In this context, certain gastroduodenal reflux enzymes can be activated in weakly acidic and alkaline environments, leading to mucosal damage and associated symptoms. The suggestion that laryngeal lesions may be due to the presence of reflux is more likely when the patient additionally reports a feeling of dry mouth, which may be related to the effect of low pH reducing the viscoelastic properties of saliva. Despite normal secretion at pH values around 4, the gel structure of saliva is destroyed, and its viscosity increases.

Damaging effects are exhibited by both acid and non-acid reflux, mainly involving weakly acidic or non-acidic gastroduodenal contents and containing, among other things, bile acids, pancreatic enzymes, water, mucus, and gas, which, despite the lack of pronounced acidity (pH > 4), can damage the mucosa of the esophagus and the upper respiratory tract.

Data indicate that dysbiosis of the esophageal, gastrointestinal, and intestinal microbiota is involved in the pathogenesis of GERD, including its non-acid and extraesophageal forms [18]. An altered esophageal and gastric microbiota profile was demonstrated in patients with GERD and NERD, with a shift toward Gram-negative bacteria [19], as well as an association between GERD and the disorders of the gut microbiota, including small intestinal bacterial overgrowth (SIBO), promoting chronic inflammation and poorer response to treatment [20]. Similar changes were described in patients with laryngopharyngeal reflux, with note being taken of the different composition of laryngopharyngeal microbiota and its modification following the treatment with proton pump or potassium inhibitors [21–24]. The involvement of the microbiota, including the gut, in the pathogenesis and perpetuation of LPR was also highlighted in the studies by Lechien et al. (2021) and Lee (2025) [25, 26].

In summary, LPRD is a disease with complex etiopathogenesis, diverse clinical picture, and difficult diagnosis. It significantly differs from GERD in terms of mechanisms, clinical presentation, and response to treatment, requiring individualization of the therapeutic approach and interdisciplinary cooperation of specialists. The current nomenclature associated with reflux diseases is presented in Tab. I.

Laryngologist's position: in otorhinolaryngology, LPS (laryngopharyngeal symptoms) and LPR (laryngopharyngeal reflux) are separated from LPRD (laryngopharyngeal reflux disease). The diagnosis of LPRD requires not only the presence of symptoms, but also objective evidence of pharyngeal reflux. Definitional framework has been included in the IFOS consensus (the "Dubai Definition") [7] while the diagnostic and therapeutic criteria have been organized by the 2024 European guidelines [6].

Gastroenterologist's position: in gastroenterology, LPRD is considered a part of EER, falling under the spectrum of GERD [2, 27].

THE DIAGNOSIS OF LARYNGOPHARYNGEAL REFLUX DISEASE

The diagnosis of LPRD remains one of the most challenging tasks for modern otolaryngology and gastroenterology. This is due to the non-specificity of the symptoms, their high variability, and the limitations of the methods used to diagnose the disease, including those related to their availability. Despite technological advances and the introduction of new diagnostic tools, the diagnosis of LPRD is still based on a multi-step approach, including clinical analysis, imaging studies, and physiological tests. Initially, clinical assessment is made by correlating the patient's reported symptoms with the laryngeal videoendoscopy images.

To reduce the subjectivity of clinical diagnosis, the two main assessment questionnaires, developed by Belafsky in 2001 and 2002, with their subsequent modifications, are still in use [28, 29]. One of these is the Reflux Symptom Index (RSI), focusing on clinical symptoms, while the other is the Reflux Finding Score (RFS) based

Tab. II. Diagnostic tests in LPRD.

EXAMINATION	PROCEDURE	APPLICABILITY	ADVANTAGES	LIMITATIONS
Questionnaires (RSI, RFS)	RSI: assessment of symptoms, RFS: assessment of lesions in laryngovideoendoscopy images	The assessment of the severity of symptoms and laryngeal imaging, the monitoring of therapy	Simple clinical tools	Subjective, cannot confirm reflux
Laryngovideoendoscopy	Assessment of the larynx and throat	First-choice examination in LPS	Easily accessible, fast	Non-specific changes, cannot confirm reflux
24-Hour esophageal pH-metry	pH drops to < 4 recorded by a sensor probe over 24 hours	Classic tool in GERD diagnosis	Simple, widely available, but no longer recommended	Detects only acid and weak acid reflux with up to 70% sensitivity; does not reach the throat; does not determine the duration or number of individual reflux episodes
24-Hour multichannel intraluminal impedance-pH monitoring MII-pH)	pH and impedance measured using a probe: acid and non-acid reflux; detects association of any complaint as reported by the patient with the presence of reflux; records postprandial reflux episodes	A standard tool in the diagnosis of GERD	Documentation of the presence and extent of acid and non-acid reflux; important in the selection of appropriate treatment; strong evidence of GERD when exposure time is more than 6% of monitoring time	No confirmation of laryngeal reflux
Hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH)	pH and impedance measured with additional sensors within the lower pharynx; reflux reaching the pharynx and larynx can be recorded	The most accurate test in the diagnosis of LPRD	Detects acid reflux and non-acid reflux and provides evidence on reflux reaching the throat/larynx	Low availability, costly, requires experience
Salivary pepsin test	Saliva samples screened for the presence of pepsin	Screening for suspected LPR, especially in laryngological practice	Non-invasive, fast	Variable sensitivity and specificity, lack of standardization
Gastroduodenoscopy	Evaluation of the appearance of the mucosa of the esophagus, cardia, stomach, and duodenum, including the retention of contents	Suspected complications of GERD	Detection of Barrett's esophagus, erosions within the distal part of the esophagus	No features specific to LPR

on laryngeal videoscopic presentation. The RSI questionnaire covers symptoms such as hoarseness or other vocal problems, grunting, excess pharyngeal secretions, difficulty swallowing, coughing after eating/lying down, difficulty breathing/dyspnea, coughing fits, globus sensation/tightness of the throat, heartburn, or burning in the chest. The severity of each symptom is assessed on a scale of 0 to 5, where 0 means none and 5 means a major problem. A score above 7 suggests a diagnosis of LPR.

With regard to clinical evaluation of changes observed on laryngovideoendoscopy (LVE) of a patient with suspected LPR, the most important tools, presenting with moderate to high accuracy and reliability, include the aforementioned RFS and the Reflux Sign Assessment-10 (RSA-10) [30–32]. The RFS relates to eight features as seen in LVE images, including swelling, congestion, hypertrophy of the posterior commissure, or the presence of granuloma and thick mucus. The score ranges from 0 to 26, with values above 13 being suggestive of LPR. The use of modern endoscopic imaging techniques, such as Narrow-Band Imaging (NBI), further increases the sensitivity of detecting inflammatory and precancerous lesions [33]. As indicated by the results of the studies, the changes observed on laryngoscopy are not specific to LPRD and can also occur in healthy individuals, smokers, singers, or patients with allergies [34, 35]. The subjectivity of the assessment and lack of standardization result in RFS being of limited value as a stand-alone diagnostic tool [32].

The RSA-10 is a newer, simplified version of the original RSA scale that facilitates rapid assessment of both laryngeal lesions and extralaryngeal symptoms. The questionnaire includes 10 items which assess, e.g., the redness of the throat, the presence of thick mucus, or changes in the oral cavity and nasopharynx. Total scores range from 0 to 40, with the score of > 13 being suggestive of LPRD. Characteristic VLE images, as acquired using a flexible endoscope, are shown in Fig. 1.

An objective test recommended for the diagnosis of LPR symptoms consists of reflux being monitored by multichannel intraluminal impedance-pH monitoring (MII-pH) (Fig. 2.). The latest ENT guidelines point to hypopharyngeal-esophageal MII-pH (HEMII-pH) as the gold standard in the diagnostics of LPRD; the method is an extension of MII-pH involving additional sensors being placed inside the pharynx to objectively document refluxate reaching the hypopharynx (hypopharyngeal episodes). The tool facilitates not only the detection of classic acid (pH < 4) reflux, but also that of weak acid (pH 4–7) and alkaline reflux (pH > 7). Above all, unlike pH-metry alone, it facilitates the assessment of the extent and direction of refluxate flow as well as its physical properties (liquid, gas, mixed-content), including in cases reaching beyond the upper esophageal sphincter, i.e., into the pharynx. This test is performed using a disposable probe less than 7 mm in diameter and featuring several impedance channels located at different heights, as well as a pH-metric sensor being inserted through the nose into the esophagus. This facilitates capturing the type, the frequency, as well as the physical and chemical properties of refluxate in real time, during the patient's usual activities, including food intake and rest [6]. The test facilitates differentiation of LPRD subtypes, which is

important for the personalization of treatment as it allows assessing whether the patient should be treated with proton pump inhibitors or perhaps alginates, hyaluronates, prokinetics, or other targeted therapies [32]. Despite its high diagnostic value, HEMII-pH remains a challenging procedure, usually available only at reference centers, and requiring proper preparation (including the withdrawal of PPIs for ≥7 days before the assessment) and experienced analysis. In practice, HEMII-pH is the key method for reliably diagnosing LPRD, especially in refractory or atypical cases [12].

Gastroduodenoscopy, while frequently ordered in the diagnosis of patients with suspected reflux, is of no importance in the diagnosis of LPRD, as most patients with LPRD are not found to present with lesions typical of GERD, such as erosions or Barrett's esophagus. On the other hand, the absence of lesions on endoscopic examination does not rule out the disease, and proximal reflux into the larynx can occur despite normal esophageal presentation. However, gastroduodenoscopy is applicable to alarm symptoms such as dysphagia, bleeding, weight loss, or suspected malignant lesions [1] (Fig. 3.).

Recent years have seen an increased interest in reflux biomarkers, especially in assays to detect pepsin in saliva (e.g., Peptest). Pepsin, an enzyme produced exclusively in the stomach, is a potential marker for the presence of reflux within the pharynx and oral cavity. The test is non-invasive, relatively inexpensive, and easy to perform. However, the results vary depending on the time of day, food intake, and the sampling technique. In addition, the absence of pepsin does not exclude the presence of LPRD, as cases in which reflux is detected by HEMII-pH while no pepsin is found in the saliva were also reported on [10, 36]. Although the pepsin assay is a promising screening tool, its role in confirming the diagnosis of LPRD remains limited and requires further validation.

In light of the above data, an accurate diagnosis of LPRD requires a combination of available tools, a carefully collected history, and the exclusion of other potential causes of the reported symptoms. The current guidelines recommend empirical treatment being implemented only in patients with a clear suspicion of LPRD and no alarm symptoms, while objective diagnostic tools, preferably HEMII-pH, are recommended for the diagnosis in the remaining cases (Tab. II.)[6, 32].

Laryngologist's position: scales such as RSI and RFS can support the assessment and monitoring, while not being capable of confirming the disease itself [6]. Laryngeal videoendoscopy is primarily used to rule out other diseases and is not sufficient to diagnose LPRD. In otorhinolaryngology, HEMII-pH should become the standard for definitive confirmation of LPRD, the diagnostic criterion consisting in the detection of at least one episode of pharyngeal reflux per day [6]. However, the availability of the tool is limited, especially outside reference centers.

Gastroenterologist's position: in line with the laryngologist's position: neither laryngovideoendoscopy nor RSI/RFS are sufficient to diagnose LPR or, according to the gastroenterology nomenclature, extraesophageal form of GERD. Symptoms should be correlated with the results of functional tests [27]. It must be emphasized that no single test is available to confirm the causality of reflux

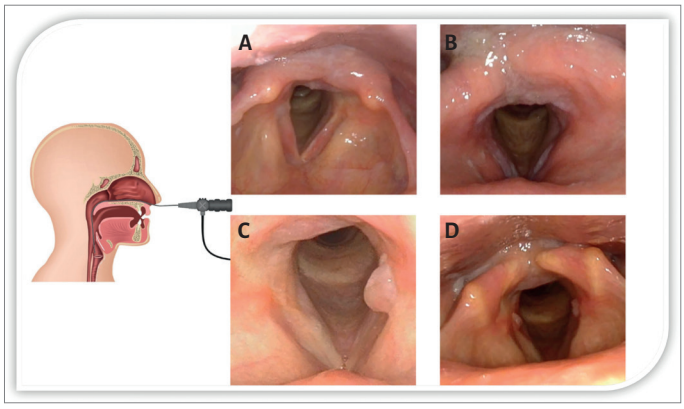

Fig. 1. Characteristic images of LPR acquired in white light endoscopy acquired using a flexible laryngeal videoendo-scope; (A) reddening of the vocal folds; (B) hypertrophy, swelling of the posterior commissure area, reddening of the mucosal membrane; (C) granuloma of the left arytenoid; (D) arytenoid granulomas, reddening of the posterior laryngeal mucosa.

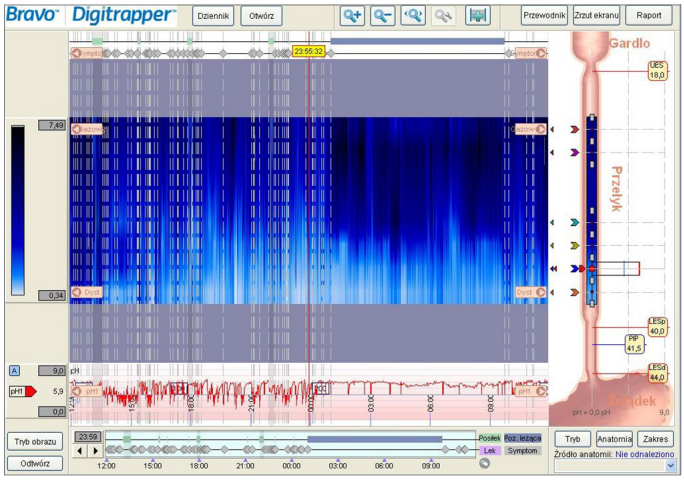

Fig. 2. A record of a 24-hour multichannel intraluminal impedance-pH monitoring (MII--pH) test in a patient with LPRD: total acid exposure unremarkable (pH usually > 4, without long episodes) while numerous episodes of weak acid/non-acid reflux reaching proximal regions, especially at night in supine position are noted.

in extraesophageal symptoms, and the diagnosis of the disease must be based on the entire presentation. Objective tools like multichannel intraluminal impedance with pH monitoring (MII-pH) or extended wireless pH monitoring for up to 96 hours and gastroscopy are preferred. The Lyon 2.0 consensus [37] defines the criteria for actionable GERD and specifies when to perform off-PPI versus on-PPI tests [27, 37].

THE TREATMENT OF LARYNGOPHARYNGEAL REFLUX DISEASE

Developing an effective and personalized treatment for laryngopharyngeal reflux disease requires a precise understanding of the pathomechanisms leading to the presented symptoms. Indeed, it should be borne in mind that LPRD is a separate disease entity, distinct from GERD, more frequently characterized by alkaline and weak acid reflux occurring in the upright position and during the daytime, without the typical heartburn and esophageal erosions [6].

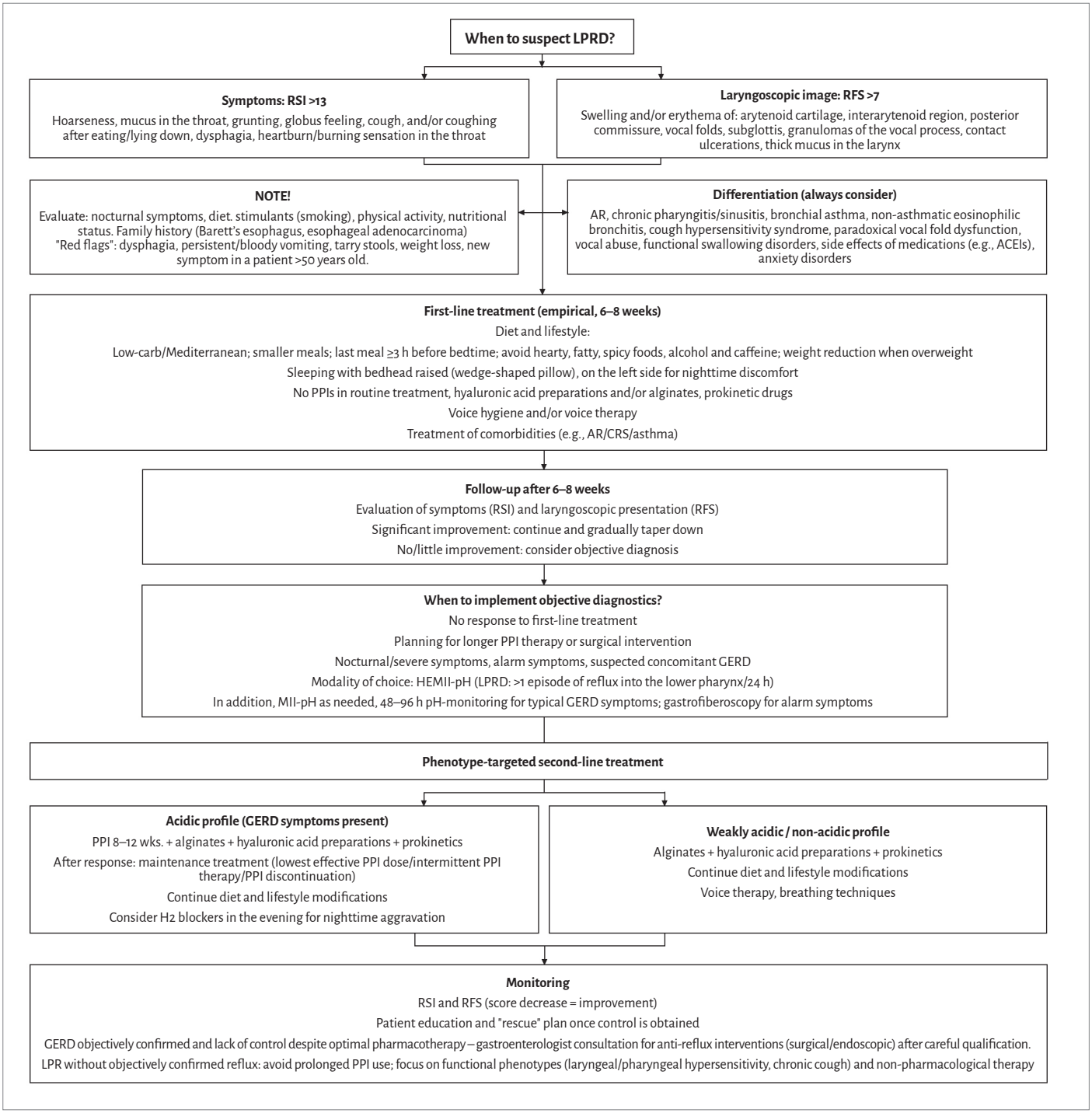

Fig. 3. Algorithm summarizing the management of LPRD according to current otolaryngological and gastroenterological guidelines and consensus [1–3, 6, 7].
ACEi – angiotensin-converting enzyme inhibitors; AR – allergic rhinitis; CRS – chronic rhinosinusitis.

Unlike GERD, the presence of lesions upon endoscopic examination of the upper gastrointestinal tract is not necessary for the diagnosis of LPRD, and the absence of erosions does not exclude the disease. Also, laryngeal videoendoscopic imaging, while useful in evaluating the laryngeal mucosa, cannot be considered sufficient for the diagnosis as many of the lesions observed are non-specific and may also occur in healthy individuals [6].

The treatment of LPRD should be based on three pillars: lifestyle modification, drug therapy, and, in strictly justified cases, surgical treatment.

The drugs to treat LPRD can be divided into several groups:

1. Proton pump inhibitors (PPIs) used mainly in acid reflux and in patients presenting with features of GERD;
2. Prokinetic agents that promote gastric emptying and strengthen the lower and upper esophageal sphincter tone;
3. Barrier/protective formulations:
   a. Alginates that break down the acid pocket within the stomach thus reducing the number of reflux episodes;
   b. Medical products with hyaluronic acid to protect the mucosa of the pharynx and the esophagus from the harmful

effects of acid and pepsin, as well as to heal any mucosal micro-damage caused thereby.

NON-PHARMACOLOGICAL MANAGEMENT

Modification of lifestyle and eating habits

Lifestyle changes are the cornerstone of LPRD treatment, regardless of pharmacotherapy implemented. The most commonly recommended interventions include avoiding meals 2–3 hours before assuming horizontal position, weight reduction in overweight or obese patients, limiting the intake of fatty foods, chocolate, alcohol, coffee, and carbonated beverages, smoking cessation, raising the head of the bed (by about 15–20 cm) or using wedge-shaped pillows and sleeping on the left side, as well as stress reduction techniques (e.g. meditation, cognitive--behavioral therapy) [6, 12].

Weight reduction, while important in GERD, may not be as important in LPRD since most patients are not obese. Even modest weight reduction and avoidance of late-night meals can be beneficial, especially in patients with mixed-type reflux or coexisting GERD. Other modifiable factors include smoking reduction, stress management, improved sleep quality, and treatment of comorbid mood disorders, which are often present in patients with LPRD [7].

At the first step, the patient should be advised to change his or her diet and daily habits to a diet rich in protein and low in fat, simple sugars, and acidic substances (such as coffee, tea, carbonated drinks, alcohol, hot spices) reducing the number of reflux episodes and salivary pepsin levels [6, 38, 39]. Many studies have shown the beneficial effects of the Mediterranean diet, rich in vegetables, fruit, fiber, and low-processed plant products. In particular, it is recommended to eliminate food that irritates the pharyngeal mucosa and reduces the tone of the lower and upper esophageal sphincter (e.g., mint, citrus fruits, hot spices). It is extremely important to make the patient aware so that they do not adopt a horizontal position for 3 hours after finishing eating.

Laryngologist's position: lifestyle and dietary modifications are the first line of treatment. Mediterranean-style plant-based diet and alkaline water may be more effective than PPIs in reducing LPS [39].

Gastroenterologist's position: weight reduction, avoiding meals 2–3 hours before bedtime, bed head elevation, and left-sided sleeping position are recommended. In EER, the evidence for the efficacy of the above management is weaker than in GERD [2, 27].

PHARMACOLOGICAL TREATMENT

The drugs to treat LPRD can be divided into several groups:

1. Proton pump inhibitors (PPIs) used mainly in acidic reflux and in patients presenting with features of GERD.
2. Prokinetic agents that promote gastric emptying and strengthen the lower and upper esophageal sphincter tone.
3. Barrier/protective formulations: alginates that break up the acid pocket within the stomach, thus reducing the number of reflux episodes, and medical products with hyaluronic acid to protect the mucosa of the pharynx and the esophagus from the harmful effects of acid and pepsin, as well as to heal any mucosal micro-damage caused thereby.

Proton pump inhibitors

In patients with chronic reflux laryngitis, PPIs remain one of the most commonly used drug types, their aim being to reduce the acidity of gastric contents and inactivate the pepsin enzyme. Although PPIs do not affect the number of reflux episodes, they reduce the aggressiveness of reflux and thus reduce its irritant effect on the pharyngeal and laryngeal mucosa. The traditional approach, as proposed by Park et al. (2005) [40], suggested that therapy be started from a twice-daily dose of PPIs (e.g., 2 × 20 mg of omeprazole daily) for 4 weeks, followed by maintenance treatment over additional weeks depending on clinical response. The power of evidence from the study was limited as it was the only randomized trial conducted on an ENT patient population comparing once-daily versus twice-daily dosing [40].

In recent years, newer studies and recommendations have emerged that are changing the attitude towards PPIs in LPRD. In an analysis of 55 studies, Lechien (2024) showed that PPIs had been used as monotherapy in 70% of cases, yet their treatment efficacy varied widely, from 17% to 87%, depending on the type of reflux (acid vs. alkaline), treatment regimen, and duration [41]. Krause and Yadlapati [12] (2024) emphasize that the lack of conclusive data supporting the efficacy of PPIs in reducing LPRD symptoms prompts their more cautious use and greater emphasis being placed on diagnosis before initiating empirical treatment. The 2024 European consensus [6] recommends that PPIs be considered only in patients with documented acid reflux or GERD symptoms coexisting with LPRD. PPI therapy should be short (up to 2 months), and its effectiveness should be regularly assessed. In cases of no improvement, changing the drug group (e.g., to barrier drugs) should be considered rather than increasing the dose [6].

PPIs are prodrugs that are activated in the acidic environment of gastric lining cells, where they irreversibly inhibit the action of proton pumps. The majority of PPIs available on the Polish market are monophasic preparations that should be taken on an empty stomach. For them to work effectively, they should have already been absorbed into the blood when the pumps are activated by the meal. Therefore, it is recommended that PPIs be taken 30–40 minutes before the first meal, as only 5–10% of pumps are active on an empty stomach as compared to up to 75% after a meal, which increases the drug's effectiveness when used properly [42].

Patient response to PPIs depends on genetic conditions, mainly polymorphisms of the CYP2C19 enzyme. Patients who metabolize the drug quickly may require higher doses or a change in formulation to achieve a good therapeutic effect [41].

Although PPIs have so far also been treated as a therapeutic test to confirm the reflux nature of symptoms, current guidelines

are moving away from this simplification. The American Gastroenterological Association and the Polish Society of Gastroeneterology [1, 2] recommend that diagnostic tests (e.g., pH-metry with impedance measurements) be pursued first, and only then, targeted drug therapy should be implemented, especially in LPRD without classic GERD symptoms.

In addition, it is worthwhile to supplement PPI therapy with prokinetics and medical devices with hyaluronic acid, as well as alginates. Laryngitis of reflux etiology is frequently caused by non-acidic refluxate, and therefore, the use of primary antisecretory treatment (PPIs) is not justified. Prokinetic drugs to improve upper gastrointestinal motility, and medical devices with hyaluronic acid to heal micro-damage to the pharyngeal and esophageal mucosa and shield against the damaging effects of refluxate play an extremely important role, albeit sometimes underestimated by clinicians.

H2-receptor antagonists (e.g., famotidine) find supportive use, especially in nocturnal symptoms. However, it is important to keep in mind the risk of tachyphylaxis, i.e., the loss of efficacy after just a few days of use, and the "rebound" effect of increased acid secretion following abrupt withdrawal of the drug [42].

While proton pump inhibitors remain one of the components of the treatment of laryngopharyngeal reflux, their use should be more selective and preceded by appropriate diagnostics. Current recommendations suggest that empirical PPI therapy may be useful only in patients with a high probability of acid reflux [6, 12]. A personalized approach seems more effective and safer, with a growing role for alginates, prokinetic drugs, hyaluronic acid preparations, and other adjunctive therapies.

Laryngologist's position: a short, time-limited course of PPIs (e.g., equivalent of 20–40mg of omeprazole b.i.d. 30 min before breakfast and dinner) is used when acid reflux is likely. These drugs should always be combined with non-pharmacological recommendations and a plan for withdrawal after improvement [6].

Gastroenterologist's position: the response to PPIs does not confirm the diagnosis. After an unsuccessful course (up to 12 weeks), objective diagnostic tests (pH-metry with impedance measurements) should follow [2].

Prokinetic drugs

An approach that targets the pathomechanism of laryngopharyngeal reflux disease is crucial in the treatment of the disorder. Prokinetic drugs, through their effect on upper gastrointestinal motility, directly affect the main causes of reflux, especially proximal non-acid reflux, frequently encountered in extraesophageal forms of GERD [11, 41]. Clinical trials confirmed the efficacy of prokinetics both in monotherapy and in combination with proton pump inhibitors. Combination therapy can help reduce symptoms faster and reduce the risk of recurrence [43–46]. Given the limited efficacy of antisecretory therapy for non-acid or gaseous reflux, it is advisable to consider implementing prokinetics from the beginning of therapy, in parallel with PPIs or even without the latter.

Itopride is currently the only prokinetic with a favorable safety profile available on the Polish market. It exhibits multifaceted effects of improving esophageal peristalsis, increasing the tone of the lower esophageal sphincter, and accelerating gastric emptying. As a result of these mechanisms, it reduces the number of transient sphincter relaxations, resulting in fewer episodes of reflux. Importantly, it works independently of the pH of the refluxate, so it can also be used in the treatment of non-acid reflux. The drug has good bioavailability and reaches maximum serum concentration about 35 minutes after oral administration, its a half-life being about 6 hours. Itopride is excreted mainly by the kidneys in the form of inactive metabolites. Food does not affect the absorption of the drug, so it does not need to be taken on an empty stomach, increasing the comfort of the treatment [41].

Adding itopride to standard PPI therapy leads to better clinical outcomes compared to monotherapy in acid reflux episodes. In a randomized, 12-week trial comparing lansoprazole (30 mg) with lansoprazole + itopride (3 × 50 mg) therapy, a significant reduction in severity as measured using the RSI scale was observed. Similar results, i.e., a reduction in symptoms such as hoarseness, coughing, and globus sensation as well as a reduction in morphological changes within the larynx as assessed by the RFS scale, were obtained in another trial involving pantoprazole (40 mg) and itopride [44, 45]. Combination treatment also significantly reduced the recurrence of symptoms after therapy [46]. The recommended dose of itopride for adults is 150 mg daily (3 × 50 mg before meals). It is used for a maximum of 6 weeks in monotherapy, and up to 12 weeks in combination with PPIs.

In addition to itopride, other prokinetics were in the treatment of LPRD, although their use is currently limited due to safety concerns: domperidone, a dopamine D2 receptor antagonist, has antiemetic and prokinetic effects, albeit limited by the risk of QT interval prolongation and arrhythmias [41]; metoclopramide, also a D2 antagonist, is not recommended for long-term use due to central and extrapyramidal effects [12]; cisapride, a 5-HT4 receptor agonist, is now virtually unavailable due to cardiovascular side effects [11].

According to European and American guidelines, prokinetics are not considered the first-line treatment in LPRD. However, they can be a valuable adjunct to therapy in patients with suspected gastric emptying disorders, diurnal symptoms, gaseous or non-acid reflux, as resistance to PPIs is observed particularly in these cases [6, 11, 12]. However, in the latest guidelines of the Polish Society of Gastroenterology addressed to family physicians, itopride has found its use not only in episodic symptoms, but also in the treatment of GERD concurrently with PPIs [3].

Prokinetics, particularly itopride, are also valuable adjuncts to the treatment of LPRD. Due to their effect on gastrointestinal motility and independence from the pH of the refluxate, they show effectiveness in both acid and non-acid reflux. Their use in combination therapy with PPIs contributes to faster symptom improvement, reduced recurrence, and improved quality of endoscopic imaging. Itopride, being a safe and well-tolerated

drug, can be successfully used in daily clinical practice, especially in the ENT patient population.

Protective/barrier preparations in laryngopharyngeal reflux disease

Protective preparations, also known as barrier preparations, are becoming increasingly important in the treatment of laryngopharyngeal reflux disease. Their function is not to inhibit gastric acid secretion, but rather to protect the mucosa against the irritant components of refluxate, such as hydrochloric acid, pepsin, and bile. The group consists mainly of alginates and hyaluronic acid (HA) preparations.

Alginates

Alginates are polysaccharides extracted from brown algae, which form a mechanical gel-like structure, i.e., a floating barrier on the surface of gastric contents and protect the esophagus and pharynx from the effects of refluxate by breaking down the so-called acid pocket within the proximal part of the stomach [47–49]. The acid pocket is a thin layer of unbuffered, highly acidic gastric juice secreted postprandially in the proximal stomach at the cardia and constituting a major source of reflux. Upon contact with acid, alginates form a floating raft that covers and displaces the acid pocket, limiting its access to the cardiac orifice and reducing exposure of the esophagus and pharynx; in addition, alginates partially dilute and thus alkalize this most acidic layer. Alginate preparations often contain neutralizing compounds such as sodium or potassium bicarbonate and calcium or magnesium carbonate, which neutralize hydrochloric acid within the raft, with the CO_2 released from bicarbonates increasing the raft's buoyancy and stability [50].

Alginates were shown to be effective in relieving the symptoms of LPRD, especially in the weak acid or alkaline reflux that is predominant in this disease entity, justifying the use of mechanically acting preparations regardless of the pH of the refluxate [51]. Alginates are particularly effective in postprandial and nocturnal reflux, when the backflow of gastric contents is most severe. They can be used as monotherapy or in combination with PPIs. According to the current position of the American Gastroenterological Association regarding extraesophageal manifestations of GERD, alginates can be used as an alternative for acid suppression alone or in combination with PPIs in appropriately selected patients [2].

As the mechanism of action of alginates is mainly gastric, they do not directly protect the pharyngeal mucosa but rather reduce the reflux process itself.

Barrier preparations with hyaluronic acid

Topical barrier preparations are an important adjunct to the treatment of both GERD and LPRD. Of particular note is a medical device with a natural, unique composition of HA, chondroitin sulfate (CS), and poloxamer 407. It provides simultaneous protection and promotes healing of the esophageal and pharyngeal mucosa as well as the upper respiratory tract previously damaged by reflux episodes [52]. The formulation can be used as monotherapy in patients with milder forms of the disease, as an add-on treatment to PPIs for symptoms that require antisecretory therapy, and as bridging therapy during periods of necessary PPI withdrawal, e.g., before diagnosis of *Helicobacter pylori* infection [53, 54]. The mechanism of action of the product is based on the synergy of three ingredients: hyaluronic acid, chondroitin sulfate, and poloxamer 407.

HA is a common component of the extracellular matrix, including within the connective tissue, skin, and synovial fluid, as well as within the mucous membranes of the gastrointestinal tract, where it co-forms the barrier and participates in repair processes. Due to its strong hydrophilic properties, it intensively moisturizes the mucosa and limits the diffusion of irritants, and through interactions with cell receptors, it modulates the inflammatory response, promotes cell migration and proliferation, and stimulates the synthesis of type III collagen as the key to scarless healing [55]. Moreover, in light of experimental data, HA may accelerate intestinal mucosal healing by interacting with TSG-6, enhancing epithelial regenerative mechanisms [56]. Chondroitin sulfate, being a natural glycosaminoglycan present in proteoglycans of the extracellular matrix (e.g., cartilage, skin, ligaments) and gastrointestinal mucosa, exhibits immunomodulatory effects, affecting cytokines, chemokines, growth factors, protease inhibitors, and adhesion molecules by its sulfate groups being capable of binding positively charged pepsin residues, limiting their damaging effects on the epithelium [52]. Poloxamer 407 is a non-ionic compound with thermoadhesive and hydrophilic properties that increase the adhesion of the formulation to moist mucosa and prolong contact time with the epithelial surface. The resulting viscous, bioadhesive film limits the contact of hydrochloric acid, pepsin, and bile salts with the mucosa. A multicenter randomized trial in patients with non-erosive GERD showed that the addition of HA/CS/poloxamer 407 to a standard PPI therapy was significantly more likely to lead to resolution or reduction of GERD symptoms compared to PPI alone, with a marked effect on reducing regurgitation and improving the quality of life while presenting with a safety profile comparable to that of placebo [53]. In an observation involving patients with LPR, a two-week treatment led to a significant decrease in the RSI and an improvement in laryngoscopic presentation (RFS), the greatest benefit being seen in combination with PPIs, especially in patients with chronic cough, grunting, and hoarseness [54].

At present, a wide range of medicinal products supporting antisecretory treatment can be encountered on the pharmaceutical market in the form of preparations that heal mucosal lesions, protect the mucosa, and neutralize the acid layer on the surface of digestive contents. In addition to the hyaluronic acid-based agent described above, a three-component preparation is recommended, which includes calcium carbonate, sodium alginate, and standardized extract of prickly pear leaves and European olive leaves (Mucosave®; Bionap) [57, 58]. While lacking chondroitin in its composition, the preparation, thanks to its properties, can be used to protect the esophageal mucosa and also prevent refluxate backflow by establishing a proper barrier.

It is worthwhile that patients be made aware not to sip any fluids after taking any barrier preparations so as not to reduce their effect.

Neutralizing agents (antacids)

Antacids neutralize acid stomach contents and can provide temporary relief from symptoms. They contain alkaline compounds (e.g., aluminum hydroxide, magnesium hydroxide, calcium carbonate) and act by directly chemically neutralizing hydrochloric acid in the stomach, leading to an increase in its pH. They can cause side effects related to ion absorption (e.g., constipation with aluminum preparations, diarrhea with magnesium preparations), and have no barrier effect on reflux. In recent years, an increase in their importance as an alternative to PPIs has been observed, especially in forms of LPRD not associated with severe acid reflux.

Laryngologist's position: alginates and hyaluronates are frequent first-line treatments or adjuncts. They have proven similarly effective to PPIs in treating LPRD [59]. IPPs should be used selectively, only in documented acid reflux, over short periods, and at the lowest effective dose [6].

Gastroenterologist's position: IPPs are essential in the treatment of GERD, while being limited in their efficacy in isolated extraesophageal symptoms; hence, escalating doses without reflux being evidenced through objective testing is not recommended. Alternatives include alginates and hyaluronates, and, less commonly, an overnight histamine H2 receptor antagonist [2, 27].

SURGICAL TREATMENT

Surgical treatment of extraesophageal reflux symptoms in patients who do not respond to suppression of gastric acid secretion by PPIs is not recommended [2]. Not all patients with reflux--related laryngological syndromes would benefit from anti-reflux surgery. Surgical interventions usually have a good effect in patients in whom high numbers of reflux episodes are recorded in impedance measurements. The number of episodes in impedance measurements alone is not a predictor of the success of surgical treatment; in isolated LPR, the efficacy is variable, hence the need for strict patient selection [10, 60, 62].

Laryngologist's position: anti-reflux surgery can be considered in patients with objectively confirmed reflux and failure of conservative treatment [6].

Gastroenterologist's position: treatment (e.g., fundoplication) is indicated only in documented GERD. The lack of response to PPIs foreshadows the lower efficacy of surgery in extraesophageal symptoms [2, 27].

SUPPORTIVE AND INTERDISCIPLINARY THERAPIES

Many LPRD patients show symptoms of laryngeal hypersensitivity, chronic muscle tension, and anxiety disorders. In such cases, benefits can be achieved by the inclusion of voice therapy and phonation rehabilitation (phoniatrist/speech therapist), psychotherapy (especially CBT – cognitive behavioral therapy), and/or physiotherapy for the neck and laryngeal muscles.

THE MONITORING OF TREATMENT

In the past, it was assumed that LPRD treatment should last 3–6 months. Recent data from prospective studies indicate that a significant group of patients (about 30%) achieve a marked reduction in symptoms after just 1 month of therapy. In other patients, treatment can be continued for up to 9 months, depending on clinical response and results of follow-up tests (e.g., RSI, RFS scales). Gradual drug tapering is recommended for patients wh achieved symptomatic remission. In cases of no improvement, it is advisable that the drug class be changed rather than increasing the dose.

CONCLUSIONS

The treatment of laryngopharyngeal reflux disease remains a diagnostic and therapeutic challenge due to its nonspecific clinical presentation and diverse pathophysiological mechanisms. Current clinical guidelines recommend a personalized approach, taking into account the type of reflux (acid, weak acid, alkaline), the severity of symptoms, and the patient's response to therapy. Treatment of LPRD requires a multidirectional approach. In recent years, the role of non-pharmacological therapies and pharmacological alternatives to classic proton pump inhibitors (PPIs) has been increasing as their effectiveness is being confirmed in new clinical trials.

In LPRD, PPIs are not routinely discontinued in favor of alginates, hyaluronates, or prokinetics; however, empirical PPI therapy is not recommended in isolated extraesophageal symptoms. It is worthwhile that reflux be documented first (e.g., by pH-impedance measurement) without IPP treatment and only then the appropriate treatment be selected [2, 12]. PPIs remain an option in patients with proven acid exposure or when typical GERD symptoms coexist. In the practice of clinical objectivization, due to the limited availability of pH-metry with impedance and the patients' expectations of achieving a quick result, first-line treatment is initiated, and a referral for further testing is issued only in the case of the former being unsuccessful.

The implementation of modern diagnostic tools and interdisciplinary cooperation increase the chances of successful treatment of this diagnostically difficult disease entity.

Current guidelines clearly indicate the need for personalized therapy for LPRD as based on accurate recognition of the nature of reflux and patient preferences. Schematic use of PPIs should be avoided, especially without confirmation of the acid nature of the reflux. The key to success lies in a balanced approach that includes patient education, lifestyle changes, and rational pharmacotherapy. The proposed algorithm sums up the current state of knowledge and the recommendations while being modeled after the guidelines of international laryngological as well as gastroenterological societies (Fig. 3.).

REFERENCES

1. Świdnicka-Siergiejko A.K., Marek T., Waśko-Czopnik D. et al.: Diagnostic and therapeutic management in gastroesophageal reflux disease: Consensus of the Polish Society of Gastroenterology. Polish Arch Intern Med., 2022; 132(2): 16196. doi: 10.20452/PAMW.16196.
2. Chen J.W., Vela M.F., Peterson K.A., Carlson D.A.: AGA Clinical Practice Update on the Diagnosis and Management of Extraesophageal Gastroesophageal Reflux Disease: Expert Review. Clin Gastroenterol Hepatol., 2023; 21: 1414–1421.e3. doi: 10.1016/j.cgh.2023.01.040.
3. Waśko-Czopnik D., Gąsiorowska A., Janiak M. et al.: Rekomendacje dla lekarzy rodzinnych dotyczące diagnostyki i leczenia choroby refluksowej przełyku. Lek POZ., 2024; 10 (4): 190–201.
4. Vakil N., Van Zanten S. V., Kahrilas P. et al.: The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol., 2006; 101(8): 1900–1920. doi: 10.1111/J.1572-0241.2006.00630.X.
5. Koufman J.A., Aviv J.E., Casiano R.R., Shaw G.Y.: Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngol Head Neck Surg., 2002; 127: 32–35. doi: 10.1067/MHN.2002.125760.
6. Lechien J.R., Chiesa-Estomba C.M., Hans S. et al.: European clinical practice guideline: managing and treating laryngopharyngeal reflux disease. Eur Arch Oto-Rhino-Laryngology., 2024. Online ahead of print. doi: 10.1007/s00405-024-09181-z.
7. Lechien J.R., Vaezi M.F., Chan W.W. et al.: The Dubai Definition and Diagnostic Criteria of Laryngopharyngeal Reflux: The IFOS Consensus. Laryngoscope., 2024; 134: 1614–1624. doi: 10.1002/lary.31134.
8. Koufman J.A.: 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: 1–78. doi: 10.1002/LARY.1991.101.S53.1.
9. Koufman J.A., Amin M.R., Panetti M.: Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. Otolaryngol Head Neck Surg., 2000; 123: 385–388. doi: 10.1067/MHN.2000.109935.
10. Lechien J.R., Akst L.M., Hamdan A.L. et al.: Evaluation and Management of Laryngopharyngeal Reflux Disease: State of the Art Review. Otolaryngol Head Neck Surg., 2019; 160: 762–782. doi: 10.1177/0194599819827488.
11. Samuels T.L., Aoun, J., Husain, I. et al.: Advances in laryngopharyngeal reflux: Etiology, diagnosis, and management. Ann. N. Y. Acad. Sci. 2024, 53–62. doi: 10.1111/nyas.15242.
12. Krause A.J., Yadlapati R.: Review article: Diagnosis and management of laryngopharyngeal reflux. Aliment Pharmacol Ther., 2024; 59: 616–631. doi: 10.1111/apt.17858.
13. Lechien J.R., Geneid A., Bohlender J.E. et al.: Consensus for voice quality assessment in clinical practice: guidelines of the European Laryngological Society and Union of the European Phoniatricians. Eur Arch Oto-Rhino-Laryngology., 2023; 280: 5459–5473. doi: 10.1007/S00405-023-08211-6.
14. Becker V., Drabner R., Graf S. et al.: New aspects in the pathomechanism and diagnosis of the laryngopharyngeal reflux-clinical impact of laryngeal proton pumps and pharyngeal pH metry in extraesophageal gastroesophageal reflux disease. World J Gastroenterol., 2015; 21: 982–987. doi: 10.3748/WJG.V21.I3.982.
15. Eckley C.A., Costa H.O.: Comparative study of salivary pH and volume in adults with chronic laryngopharyngitis by gastroesophageal reflux disease before and after treatment. Braz J Otorhinolaryngol., 2006; 72: 55–60. doi: 10.1016/S1808-8694(15)30035-5.
16. Lechien J.R.: Minimum Effective Duration of Laryngopharyngeal Reflux Disease Treatment: A Prospective Study. Otolaryngol Head Neck Surg., 2024; 171(4): 1114–1122. doi: 10.1002/ohn.878.
17. Barry D.W., Vaezi M.F.: Laryngopharyngeal reflux: More questions than answers. Cleve Clin J Med., 2010; 77: 327–334. doi: 10.3949/CCJM.77A.09121.
18. Guan Y., Cheng H., Zhang N. et al.: The role of the esophageal and intestinal microbiome in gastroesophageal reflux disease: past, present, and future. Front Immunol., 2025; 16: 1558414. doi: 10.3389/FIMMU.2025.1558414.
19. Sugihartono T., Fauzia K.A., Miftahussurur M. et al.: Analysis of gastric microbiota and Helicobacter pylori infection in gastroesophageal reflux disease. Gut Pathog., 2022; 14: 1–9. doi: 10.1186/S13099-022-00510-3.
20. Hu Z., Shan B., Wang Y. et al.: Association of gastroesophageal reflux disease with small intestinal bacterial overgrowth: a case-control study. BMC Gastroenterol., 2025; 25: 753. doi: 10.1186/S12876-025-04291-2.
21. Chen H., Wang H., Yang F., Wang M., Chen X.: Distinct microbiota dysbiosis in patients with laryngopharynx reflux disease compared to healthy controls. Eur Arch Otorhinolaryngol., 2022; 279: 3569–3579. doi: 10.1007/S00405-022-07327-5.
22. Zhang J., Fan X.: Analysis on the pharyngeal microbiota in patients with laryngopharyngeal reflux disease. Braz J Otorhinolaryngol., 2023; 89(6): 101331. doi: 10.1016/j.bjorl.2023.101331.
23. Cui X., Yin L., Zhang Y. et al.: Salivary microbiota composition before and after use of proton pump inhibitors in patients with laryngopharyngeal reflux: a self-control study. BMC Oral Health., 2024, 24 (1):1194. doi: 10.1186/S12903-024-05000-3.
24. Zheng X., Zheng Y., Chen T. et al.: Effect of Laryngopharyngeal Reflux and Potassium-Competitive Acid Blocker (P-CAB) on the Microbiological Comprise of the Laryngopharynx. Otolaryngol Head Neck Surg., 2024; 170: 1380–1390. doi: 10.1002/OHN.682.
25. Lechien J.R., Bobin F., Dapri G. et al.: Hypopharyngeal-Esophageal Impedance-pH Monitoring Profiles of Laryngopharyngeal Reflux Patients. Laryngoscope., 2021; 131: 268–276. doi: 10.1002/LARY.28736.
26. Lee J.G.: Microbiota, Gut Health, and Laryngopharyngeal Reflux Disease. Otolaryngol Clin North Am., 2025; 58: 433–440. doi: 10.1016/J.OTC.2024.09.006.
27. Katz P.O., Dunbar K.B., Schnoll-Sussman F.H. et al.: ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol., 2022; 117: 27–56. doi: 10.14309/AJG.0000000000001538.
28. Belafsky P.C., Postma G.N., Koufman J.A.: The validity and reliability of the reflux finding score (RFS). Laryngoscope., 2001; 111: 1313–1317. doi: 10.1097/00005537-200108000-00001.
29. Belafsky P.C., Postma G.N., Koufman J.A.: Validity and Reliability of the Reflux Symptom Index (RSI). J Voice., 2002; 16: 274–277. doi: 10.1016/S0892-1997(02)00097-8.
30. Jahshan F., Ronen O., Qarawany J. et al.: Inter-Rater Variability of Reflux Finding Score Amongst Otolaryngologists. J Voice., 2022; 36: 685–689. doi: 10.1016/J.JVOICE.2020.07.021.
31. Vance D., Alnouri G., Shah P. et al.: The Validity and Reliability of the Reflux Finding Score. J Voice., 2023; 37: 92–96. doi: 10.1016/J.JVOICE.2020.11.008.
32. Lechien J.R., De Marrez L.G., Finck C., Saussez S.: Validity and Reliability of the Reflux Sign Assessment-10 (RSA-10). Laryngoscope., 2024; 134: 3981–3988. doi: 10.1002/lary.31420.
33. Popek B., Bojanowska-Poźniak K., Tomasik B. et al.: Clinical experience of narrow band imaging (NBI) usage in diagnosis of laryngeal lesions. Otolaryngol Pol., 2019; 73: 18–23. doi: 10.5604/01.3001.0013.3401.
34. Vaezi M.F., Hicks D.M., Abelson,T.I., Richter J.E.: Laryngeal signs and symptoms and gastroesophageal reflux disease (GERD): A critical assessment of cause and effect association. Clin Gastroenterol Hepatol., 2003; 1: 333–344. doi: 10.1053/S1542-3565(03)00177-0.
35. Branski R.C., Bhattacharyya N., Shapiro J.: The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. Laryngoscope., 2002; 112: 1019–1024. doi: 10.1097/00005537-200206000-00016.
36. Pillutla P., Zhang Z., Kreiman J., Wilhalme H., Chhetri D.K.: Effects of Laryngeal Vibratory Asymmetry and Neuromuscular Compensation on Voice Quality. Laryngoscope., 2022; 132: 130–134. doi: 10.1002/lary.29724.
37. Gyawali C.P., Yadlapati R., Fass R. et al.: Updates to the modern diagnosis of GERD: Lyon consensus 2.0. Gut., 2024; 73: 361–371. doi: 10.1136/GUTJNL-2023-330616.
38. Koufman J.A.: Low-acid diet for recalcitrant laryngopharyngeal reflux: therapeutic benefits and their implications. Ann Otol Rhinol Laryngol., 2011; 120: 281–287. doi: 10.1177/000348941112000501.
39. Zalvan C.H., Hu S., Greenberg B., Geliebter J.: A Comparison of Alkaline Water and Mediterranean Diet vs Proton Pump Inhibition for Treatment of Laryngopharyngeal Reflux. JAMA Otolaryngol Head Neck Surg., 2017; 143: 1023–1029. doi: 10.1001/JAMAOTO.2017.1454.

40. Park W., Hicks D.M., Khandwala F. et al.: Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. Laryngoscope., 2005; 115: 1230–1238. doi: 10.1097/01.MLG.0000163746.81766.45.
41. Lechien J.R.: Pharmacological and Biological Relevance in the Medical Treatment of Laryngopharyngeal Reflux: A State-of-the-Art Review. J Voice., 2024: 1–16. Online ahead of print. doi: 10.1016/j.jvoice.2024.11.014.
42. Gąsiorowska A., Janiak M., Waśko-Czopnik D. et al.: Postępowanie u pacjentów z objawami choroby refluksowej przełyku – rekomendacje dla lekarzy rodzinnych. Lek POZ., 2019; 5: 245–265.
43. Talley N.J., Tack J., Ptak T., Gupta R., Giguère M.: Itopride in functional dyspepsia: results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. Gut., 2008; 57: 740–746. doi: 10.1136/GUT.2007.132449.
44. Kim Y.S., Kim T.H., Choi C.S. et al.: Effect of itopride, a new prokinetic, in patients with mild GERD: a pilot study. World J Gastroenterol., 2005; 11: 4210–4214. doi: 10.3748/WJG.V11.I27.4210.
45. Chun B.J., Lee D.S.: The effect of itopride combined with lansoprazole in patients with laryngopharyngeal reflux disease. Eur Arch Otorhinolaryngol., 2013; 270: 1385–1390. doi: 10.1007/S00405-012-2341-8.
46. Ezzat W.F., Fawaz S.A., Fathey H., El Demerdash A.: Virtue of adding prokinetics to proton pump inhibitors in the treatment of laryngopharyngeal reflux disease: Prospective study. J Otolaryngol Head Neck Surg., 2011; 40: 350. doi: 10.2310/7070.2011.100196.
47. Rohof W.O., Bennink R.J., Smout A.J.P.M., Thomas E., Boeckxstaens G.E.: An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol., 2013; 11: 1585–1591. doi: 10.1016/J.CGH.2013.04.046.
48. De Ruigh A., Roman S., Chen J., Pandolfino J.E., Kahrilas P.J.: Gaviscon Double Action Liquid (antacid & alginate) is more effective than antacid in controlling post-prandial oesophageal acid exposure in GERD patients: a double-blind crossover study. Aliment Pharmacol Ther., 2014; 40: 531–537. doi: 10.1111/APT.12857.
49. Deraman M.A., Abdul Hafidz M.I., Lawenko R.M. et al.: Randomised clinical trial: the effectiveness of Gaviscon Advance vs non-alginate antacid in suppression of acid pocket and post-prandial reflux in obese individuals after late-night supper. Aliment Pharmacol Ther., 2020; 51: 1014–1021. doi: 10.1111/APT.15746.
50. Kwiatek M.A., Roman S., Fareeduddin A., Pandolfino J.E., Kahrilas P.J.: An alginate-antacid formulation (Gaviscon Double Action Liquid) can eliminate or displace the postprandial "acid pocket" in symptomatic GERD patients. Aliment Pharmacol Ther., 2011; 34: 59–66. doi: 10.1111/J.1365-2036.2011.04678.X.
51. Cui N., Dai T., Liu Y. et al.: Laryngopharyngeal reflux disease: Updated examination of mechanisms, pathophysiology, treatment, and association with gastroesophageal reflux disease. World J Gastroenterol., 2024; 30: 2209–2219. doi: 10.3748/wjg.v30.i16.2209.
52. Palmieri B., Merighi A., Corbascio D. et al.: Fixed combination of hyaluronic acid and chondroitin-sulphate oral formulation in a randomized double blind, placebo controlled study for the treatment of symptoms in patients with non-erosive gastroesophageal reflux. https://www.europeanreview.org/article/6160 (11.11.2025).
53. Savarino V., Pace F., Scarpignato C. et al.: Randomised clinical trial: mucosal protection combined with acid suppression in the treatment of non-erosive reflux disease – efficacy of Esoxx, a hyaluronic acid-chondroitin sulphate based bioadhesive formulation. Aliment Pharmacol Ther., 2017; 45: 631–642. doi: 10.1111/APT.13914.
54. Chmielecka-Rutkowska J., Tomasik B., Pietruszewska W.: The role of oral formulation of hyaluronic acid and chondroitin sulphate for the treatment of the patients with laryngopharyngeal reflux. Otolaryngol Pol., 2019; 73: 38–49. doi: 10.5604/01.3001.0013.5776.
55. Volpi N., Schiller J., Stern R., Soltes L.: Role, metabolism, chemical modifications and applications of hyaluronan. Curr Med Chem., 2009; 16: 1718–1745. doi: 10.2174/092986709788186138.
56. Sammarco G., Shalaby M., Elangovan S. et al.: Hyaluronan Accelerates Intestinal Mucosal Healing through Interaction with TSG-6. Cells., 2019, 8(9): 1074. doi: 10.3390/CELLS8091074.
57. Komolafe K., Komolafe T.R., Crown O.O. et al.: Natural Products in the Management of Gastroesophageal Reflux Disease: Mechanisms, Efficacy, and Future Directions. Nutrients., 2025, 17(6): 1069. doi: 10.3390/NU17061069.
58. Lehner M.D., Scheyhing U., Elsässer J.: A combination of carbonates and Opuntia ficus-indica extract protects esophageal cells against simulated acidic and non-acidic reflux in vitro. Sci Rep., 2024, 14(1): 22355. doi: 10.1038/S41598-024-74047-7.
59. Pizzorni N., Ambrogi F., Eplite A. et al.: Magnesium alginate versus proton pump inhibitors for the treatment of laryngopharyngeal reflux: a non-inferiority randomized controlled trial. Eur Arch Otorhinolaryngol., 2022; 279: 2533–2542. doi: 10.1007/S00405-021-07219-0.
60. Patel A., Sayuk G.S., Gyawali C.P.: Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol., 2015; 13: 884–891. doi: 10.1016/J.CGH.2014.08.029.
61. Vaiciunaite D., Eriksson S.E., Sarici I.S. et al.: The Utility of Symptom Association Probability (SAP) in Predicting Outcome After Laparoscopic Fundoplication in Patients with Abnormal Esophageal Acid Exposure. J Gastrointest Surg., 2023; 27: 2014–2022. doi: 10.1007/s11605-023-05753-2.