ARTYKUŁ PRZEGLĄDOWY / REVIEW ARTICLE

Extraesophageal manifestations of gastroesophageal reflux disease – pathophysiology, diagnosis and management

Pozaprzełykowe objawy choroby refluksowej przełyku – patofizjologia, diagnostyka i leczenie

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ABSTRACT: Gastroesophageal reflux disease (GERD) is defined as a condition in which the reflux of stomach contents causes troublesome symptoms and/or complications. This common disease may also present with atypical, extraesophageal symptoms. Laryngopharyngeal reflux (LPR) is the reflux of gastric contents into the throat and larynx, which causes symptoms such as globus, throat clearing, hoarseness and chronic cough. GERD and LPR may be related to many diseases, including laryngitis, asthma, COPD, chronic rhinosinusitis, otitis media, dental erosions, and even laryngeal cancer or life-threatening events. The diagnosis of LPR is based on clinical symptoms (measured by RSI), laryngoscopic signs (evaluated in RFS), an empiric trial of proton pomp inhibitor (PPI) therapy, 24-hour pH monitoring, impedance monitoring, esophageal manometry and endoscopic examination. The most common management is double-dose PPI therapy for at least six months. When this treatment is ineffective, the surgery should be considered. However, diagnosis and treatment of LPR is still controversial. Further studies are necessary to establish an optimal algorithm for the management of LPR.

KEYWORDS: gastroesophageal reflux disease, laryngopharyngeal reflux, extraoesophageal reflux, proton pomp inhibitors, pathophysiology, diagnosis, management

STRESZCZENIE: Chorobę refluksową przełyku (GERD) definiuje się jako stan, w którym cofanie się zawartości żołądka prowadzi do powstawania uciążliwych objawów i/lub powikłań. Ta często występująca choroba może manifestować się również objawami atypowymi, spoza układu pokarmowego. Refluks krtaniowo-gardłowy (LPR) to wsteczne napływanie zawartości żołądka do gardła i krtani prowadzące do powstania objawów, takich jak uczucie ciała obcego w gardle, odchrząkiwanie, chrypka i przewlekły kaszel. GERD i LPR mogą mieć też wpływ na rozwój wielu chorób, m.in. zapalenia krtani, astmy, POChP, przewlekłego zapalenia zatok przynosowych, zapalenia ucha środkowego czy ubytków (erozji) zębowych, a nawet raka krtani czy stanów nagłego zagrożenia życia. W diagnostyce LPR stosuje się skale oparte na objawach podmiotowych (RSI) i laryngoskopowych (RFS), próbę leczenia inhibitorami pompy protonowej (IPP), 24-godzinną pH-metrię przełyku, badania impedancji przełykowej, manometrię przełyku oraz badanie endoskopowe. Najczęściej stosowaną metodą leczenia jest podawanie IPP w podwójnej dawce przez okres co najmniej 6 miesięcy. W razie braku skuteczności farmakoterapii, można rozważyć leczenie chirurgiczne. W literaturze wciąż istnieje wiele kontrowersji odnośnie do diagnostyki i leczenia LPR. Opracowanie skutecznych algorytmów postępowania w tej jednostce chorobowej wymaga prowadzenia dalszych badań.

SŁOWA KLUCZOWE: choroba refluksowa przełyku, refluks krtaniowo-gardłowy, refluks pozaprzełykowy, inhibitory pompy protonowej, patofizjologia, diagnostyka, leczenie

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1. INTRODUCTION

Gastroesophageal reflux (GER) can be physiological and it affects most of the population, especially after meals. According to the Montreal classification, gastroesophageal reflux disease (GERD) is defined as a condition in which the regurgitation of gastric contents produces troublesome symptomes and/or complications. To be described as troublesome, symptoms must occur at least once a week and influence the quality of life. [7,90,97]

GERD typically presents with esophageal symptoms such as Heartburn, regurgitation, eructation, sometimes also nausea, vomiting, dysphagia and upper abdominal pain. However, when acid gastric contents pass the upper pharyngeal sphincter, they may evoke extraesophageal symptoms, the condition called the extraoesophageal reflux (EOR). In the Montreal consensus, extraesophageal symptoms were divided into two groups – with established and proposed association with GERD. The most common extraesophageal manifestations of GERD include: chronic cough, asthma and laryngitis (Table 1). It was emphasized that these symptoms have heterogeneous etiology and GERD is one of their risk factors rather than direct cause. [18,47,90,92]

The association of various symptoms with GERD has been reported in the literature, therefore it seems reasonable to include gastroesophageal reflux in differential diagnosis of many diseases. (Table 2)

In children, GERD may present with failure to thrive, recurrent respiratory papillomatosis (RPR), chronic cough, hoarseness, esophagitis, asthma, recurrent otitis media, vocal fold granuloma and papilloma, allergic rhinitis. Symptoms of reflux differ with child's age. Infants typically show regurgitation, vomiting, dysphagia, difficult feeding, poor weight gain, restlessness and irritation, stridor, apnea, recurrent laryngitis, laryngomalacia, subglottic stenosis, anaemia, hypoproteinaemia. In this age group, GERD may lead to an apparent life-threatening episode (ALTE). In preschool age, symptoms of GERD include: upper abdominal pain, dyspnea, sore throat, halitosis, globus sensation and recurrent pneumonia. [66,94]

Laryngopharyngeal reflux (LPR) is defined as back-flow of gastric contents into the pharynx and larynx, producing syndromes such as globus, throat clearing, chronic cough and hoarseness. The term is often used as a synonym for EOR. [14,61,64,97]

The characteristic features of reflux are different in LPR and GERD. LPR usually occurs during daytime when the patient takes a standing position, while on the other hand, GERD

Tab. I. GERD and related syndromes, according to Montreal definition. [90]

ESOPHAGEAL SYNDROMES	EXTRAESOPHAGEAL SYNDROMES
Sets of symptoms: ♦ typical reflux syndrome ♦ chest pain syndrome	with confirmed association: ♦ cough ♦ asthma ♦ laryngitis ♦ dental erosions
Syndromes with esophageal damage: ♦ esophagitis ♦ esophageal stenosis ♦ Barrett's esophagus ♦ adenocarcinoma	with possible association: ♦ sinusitis ♦ pulmonary fibrosis ♦ pharyngitis ♦ recurrent otitis media

Tab. II. Symptoms possibly related to GER [60,61,68,91]

Pharynx	Globus sensation
	Pharyngitis, sore throat
	Throat clearing, excess of mucus in throat
	Dry throat
Larynx	Chronic laryngitis, posterior laryngitis
	Dysphonia, hoarseness
	Ulceration, granulomas and vocal fold nodules
	Subglottic stenosis
	Laryngospasm
	Cancer
Nose and paranasal sinuses	Chronic sinusitis
	Nasal congestion
Ear	Otitis media with effusion
	Otalgia
Oral cavity	Dental erosions
	Aphthous ulcers
	Fetor ex ore (halitosis)
	Hypersalivation
Lower respiratory tract	Asthma
	Chronic cough
	Tracheobronchitis
	Aspiration pneumonia
	Pulmonary fibrosis
	Chronic bronchitis
	COPD
	Bronchiectasis
Other	Chest pain
	Sinus arrhythmia
	Sleep apnea
	SIDS
	Sandifer syndrome (torticollis)

Tab. III. Clinical presentation and etiopathogenesis of LPR and GERD [61]

	LARYNGOPHARYNGEAL REFLUX	GASTROESOPHAGEAL REFLUX DISEASE (GERD)
Symptoms	atypical (not related to GI tract)	typical (related to GI tract)
Time of onset	during day	at night
Positions, in which symptoms are present	standing	lying
Site of damage	upper esophageal sphincter	lower esophageal sphincter
Compensation mechanisms	none	peristalsis, flow of saliva
Predisposing conditions	glottic injury	connective tissue diseases, neurological disorders

manifests itself at night with the patient lying down. Interestingly, those patients present a different body composition. A relationship between GERD and obesity has been established, however, no such relation has been reported in patients with pharyngeal and laryngeal symptoms. [14,64,97]

As described below, prolonged exposition to acid contents is not seen in patients with LPR, and the results of diagnostic studies show that the number and time of reflux episodes remain within normal limits. For this reason, it is possible to develop injuries to the fragile mucous lining of the pharynx and larynx, despite the lack of symptoms such as Heartburn or esophagitis. It is commonly assumed that the primary cause of GERD is dysfunction of the lower esophageal sphincter, while LPR is caused by dysfunction of the upper esophageal sphincter. [64,68]

Distinction between GERD and LPR is supported by the following facts:

- 1) rare occurrence of esophagitis in patients with atypical symptoms;
- 2) rare occurrence of Heartburn and regurgitation in LPR;
- 3) negative results of esophageal biopsy in LPR;
- 4) pathological results of pharyngeal pH monitoring;
- 5) presence of GERD symptoms at night, while those of LPR – during daytime;
- 6) rare occurrence of dysphonia in GERD. [61]

The differences between GERD and LPR are summarized in Table 3.

2. EPIDEMIOLOGY

The studies performed in the USA showed that GERD is present in 20% of the population, approximately 50% of people experience Heartburn at least once a month, and 5-7% display symptoms relating to GERD every day. [18] National Cancer Institute of the United States data show that the incidence of esophageal cancer – a possible complication of GERD – increased six times between 1975 and 2001. [70]

Due to variety of clinical presentation, the true prevalence of GERD in patients with pharyngeal disorders is hard to establish and it differs between studies. [18] Altman et al. [2] reported an increase in GERD-related otolaryngological consultation rate from 1.7% (1990) to 4.7% (2001). The prevalence of GERD in patients with laryngeal stenosis is estimated to be 78%, with reflux laryngitis – 60%, globus sensation – 58%, chronic cough – 52%. [46]

In infancy, reflux is a common phenomenon and affects 1 in 500 livebirths, slightly more often in males. In infants, reflux may be physiological and recedes in the second year of life. This age group is particularly predisposed to reflux due to 5-8 times greater ratio of feed volume to body mass, smaller volume of the stomach (5-10ml compared to 180ml on average in adults) and significantly shorter intraabdominal portion of the esophagus. Children with bronchopulmonary dysplasia, tracheoesophageal fistula, laryngomalacia, neurological disorders, colon interposition and those who have undergone surgical treatment for esophageal atresia are especially at risk for developing gastroesophageal reflux. [11,47]

3. PATHOPHYSIOLOGY

Two factors in human evolution made our species particularly prone to experience reflux of gastric contents into the respiratory tract. Firstly, the relatively rapid shift to standing position was not accompanied by compensatory changes to the alimentary tract. In other mammals, the esophagus is positioned almost horizontally and food falls into the vertically suspended stomach. In humans, however, the upper portion of the gastrointestinal tract is straight, thus the anatomical barrier, which prevented the regurgitation of gastric contents during opening of the lower esophageal sphincter, is lost. The crura of the diaphragm only partially compensate for this by

curving the lower portion of the esophagus. Secondly, the descent of the larynx and separation of the soft palate from the epiglottis and arytenoid cartilages, which was associated with development of speech and caused the oropharynx to remain permanently open, allow food to fall into the respiratory tract from both the oral cavity and the stomach. [60]

Despite those evolutionary predisposing factors, the gastroesophageal reflux is not readily seen in all humans. There are certain barriers which prevent displacement of gastric contents into the respiratory tract, these include the lower esophageal sphincter (LES), peristalsis that clears the lumen, saliva, gravity and the upper esophageal sphincter (UES). When these barriers fail, it allows for direct contact of gastric contents with the mucosa of the larynx and pharynx, leading to epithelial damage, dysfunction of cilia, inflammation and loss of sensitivity. [14,60].

Patients with hiatus hernia are more prone to GERD due to abnormal location of the lower esophageal sphincter in the thorax and consequent loss of diaphragmatic component of the sphincter tone. [60] Hypotonia of the UES and increased frequency of transient lower oesophageal sphincter relaxation (TLOSR) may contribute to development of reflux. [60]

The research shows no significant difference in the frequency of reflux episodes when measured with esophageal manometry. However, the episodes are more often associated with decreased pH, which suggests that the key element in developing GERD symptoms is the acidity of the reflux contents. The return to normal pH in the esophagus is faster in case of LPR without GERD, compared to patients with GERD, and pH seems to have no influence on opening of the UES, which in turn is usually associated with TLOSR episodes and changes in intraesophageal pressure. [60] Normal pH was reported in one third of patients with chronic cough despite abnormal results of esophageal manometry. [41] The studies indicate different pathophysiological mechanism in development of classic GERD (associated rather with LES hypotonia and anatomical factors) and LPR, in which case non-acidic gaseous reflux related to TLOSR episodes plays an important role. [60] The studies showed presence of reflux with detectable gaseous component in more than 1/3 of healthy individuals. Obviously, gaseous contents reach the proximal part of the esophagus more easily than fluids and this may indicate its greater role in development of reflux into the upper airways. For this reason, the role of sole drop in pH in developing LPR is questionable, because pH of gaseous contents can be slightly acidic. [60]

Two mechanisms may be responsible for extraesophageal symptoms of GERD: direct irritation of the respiratory tract mucosa by gastric contents and indirect mechanism by means of the vagal nerve reflex. Failure of defense mechanisms can lead to irritation of the mucous membrane of the pharynx and larynx by gastric contents, but also it may involve the lower respiratory tract through microaspirations, causing laryngitis, chronic cough and asthma. The indirect mechanism stems from the fact that the esophagus and bronchi share the same embryological innervation by the vagus nerve. The presence of acidic substance in the distal part of the esophagus may stimulate acid-sensitive receptors triggering the esophageal-tracheobronchial reflex, thus producing chest pain, cough, laryngospasm, bronchial spam and asthma. The vagal response can also be elicited by irritation of the mucous membrane of the upper respiratory tract. [18,90,91]

In the direct mechanism, it is essential that the mucous membrane of the respiratory tract is more vulnerable to injury than that of the esophagus. It is due to the lack of mechanism of clearing from reflux contents, as well as intracellular defense mechanism. Even 50 episodes of reflux per day are considered normal in the esophagus, while in the larynx and pharynx a single episode can produce symptoms. [18]

Carbonic anhydrase III plays an important protecting role in the epithelium by active excretion of bicarbonates, thus regulating pH in response to acidic reflux. [14,60] In the studies, an increased activity of carbonic anhydrase III was reported in the esophagus of patients suffering from GERD, while the activity decreased in patients with LPR. [4]

Furthermore, saliva contributes to neutralization of acidic reflux contents due to its alkaline properties. [11]

Impedance-pH monitoring confirms episodes of non-acidic or slightly acidic gastroesophageal reflux in patients with symptoms of LPR, which suggests that damage to the mucous membrane may be caused not only by drop in pH, but also by exposition to substances in gastric contents such as pepsin, bile salts and pancreatic enzymes. [14]

Pepsin is actively transported into the epithelial cells of the larynx and remains stable in pH 7.4, however, it becomes irreversibly inactivated in pH 8. After reactivation of pepsin following a decrease in pH from 7.4 to 3, 72% activity of pepsin is observed, and the greatest activity is detected in pH 2. Remaining in a stable state in the larynx, pepsin can be activated during following reflux episodes or by hydrogen ions from other sources like food. Also, evidence is present that the enzyme can cause intracellular damage, because organelles such as Golgi apparatus or lysosomes have a low pH (5 and 4 respectively). [14] In the study conducted by Johnston et al. [39], the

Western blot analysis detected intracellular pepsin in 8 out of 9 biopsies of the larynx from patients with LPR and in not a single patient from control group. The presence of pepsin in tissue is associated with a decrease in key protecting proteins such as carbonic anhydrase, E-cadherin and Sep70 (epithelium stress protein). [38]

Reflux of gastroduodenal contents also contains bile acids and pancreatic enzymes. Sasaki et al. established in a study on rats that the maximum damage to the mucous membrane of the larynx takes place in pH 1.5 in case of taurocholic acid, and in pH 7.4 for chenodeoxycholic acid, which indicates that bile acids can cause laryngitis in both acidic and neutral pH. [14,76]

Moreover, Sereg-Behar et al. [78] reported higher concentration of pepsin and bile acids in the saliva of patients with laryngeal cancer, which may suggest a role of LPR in cancerogenesis. [60]

In the indirect mechanism, activation of afferent sensory nerves in the esophagus triggered by reflux contents may stimulate subpopulation of neurons in the central nervous system, which mediate defense reflexes such as cough or bronchospasm. [65] Cough is a physiological defense mechanism and is transmitted by transient receptor potential channels (TRP) in sensory neurons of the respiratory tract. An example is vanilloid receptor (TRPV1) found in the airways, which can be activated by acids, and it may explain the stimulation of cough during episodes of acidic reflux. Molecularly similar ankyrin receptor (TRPA1) is coexpressed with TRPV1 and it is stimulated by other substances like food matter, which may be important in non-acidic reflux (Fig.1). Increased expression of TRPV1 was found in patients with chronic cough [59] and those with esophagitis. [56] The research showed a decrease in frequency of coughing after administration of TRPV1 antagonists [89], which may be important in future therapies. [60]

Patterson et al. [65] describe nervous connections between the esophagus and the respiratory tract through non-adrenergic non-cholinergic (NANC) neurons, activation of which triggers axon reflex and release of neuropeptides into the airways, leading to neurogenic inflammation. Tachykinins, such as substance P (SP) and neurokinin A (NKA), are neurokinins most frequently associated with axon reflexes and they constitute strong mediators of cough, bronchospasm, increased capillary permeability and mucus production. Increased level of tachykinins was found in patients with coexisting reflux and respiratory symptoms (asthma or cough), which suggests activation of sensory neurons in the respiratory tract in this population.

On the other hand, cough can predispose to reflux by means of increased intraabdominal pressure with concurrent negative intrathoracic pressure, as well as relaxation of the LES, and hence facilitate passage of reflux contents by this barrier. [68,79,90] Furthermore, Sifrim et al. [79] reported positive the mechanism of the "vicious circle" in which an episode of reflux can cause cough, while cough can intensify reflux.

The influence of *Helicobacter pylori* infection on extraesophageal symptoms of GERD is also being studied. *H. pylor*i is primarily localized in the mucous membrane of the stomach. Its presence in paranasal sinuses, tonsils, middle ear, dental plaque and saliva has also been reported, however, other studies do not confirm it, which may indicate only temporal colonization in those locations. [97]

Siupsinskiene et al. [80] reported that *H. pylori* was found more frequently in larynx specimens in patients with laryngitis and laryngeal cancer.

In a study assessing treatment of LPR in patients infected with *H. pylori,* presence of Hp antigen in stool was determined to be 57% in patients with LPR. In that study, significantly better results of treatment were reported for triple therapy with esomeprazole, amoxicillin and clarithromycin (improvement in 90% of the patients), compared to monotherapy with esomeprazole (improvement in 40% of patients), which suggests that a possibility of *H. pylori* infection should be considered in managing LPR. [98]

However, there are also studies, which do not confirm the relationship between *H. pylori* infection and LPR. [15,25]

4. LPR – LARYNGEAL SYMPTOMS, DIAGNOSIS AND MANAGEMENT

The most common clinical manifestation of LPR is reflux laryngitis. The most common symptoms of LPR include hoarseness (especially intensive in the morning), prolonged period of morning "warm-up" of voice (more than 25 minutes), sore throat, excessive secretion in throat, post-nasal drip, throat clearing, globus sensation and cough. It is estimated that GERD accounts for symptoms in 10% of patients with hoarseness and even 60% of patients with chronic laryngitis and treatment-resistant sore throat. [90,91]

It should be emphasized that those symptoms have heterogeneous etiology and may be caused by recent infection, smoking, overusing voice and allergy; they can also be missing. Making right diagnosis based on medical history is therefore challenging. On the other hand, even in patients with the above-mentioned symptoms but no laryngoscopic signs, signs of reflux

are sometimes detected using pH monitoring. [68] For this reason, patients with chronic laryngitis without abnormalities on laryngoscopic examination should be referred for further investigation of gastroesophageal reflux. [18]

Dysfunction of voice may accompany laryngitis even when lacking other symptoms. Dysphonia in LPR is a result of abnormal mucosal wave and dysfunction of arytenoid muscle with development of gap in the interarytenoid region, which leads to compensatory spasm of the muscles and impairment of the dynamics of the larynx. GERD can be one of the causative factors of so-called muscle tension dysphonia (MTD). In this disorder, excessive contraction of the perilaryngeal and suprahyoid muscles is noticed, along with visible elevation of the larynx with raising voice, open space between the arytenoid cartilages (glottic insufficiency) and various lesions of the mucosa such as vocal fold nodules. They are often associated with increased tension of the neck and arm muscles. [40]"

Globus sensation in GERD may be caused by a few factors, including inflammation and edema of the mucous membrane of the pharynx and larynx as a result of direct irritation by gastric contents, inflammation of the pharyngeal mucosa, and reflex spasticity of the upper esophageal sphincter.

GERD was diagnosed in 75% of patients with chronic sensation of excessive secretion in throat. After 4-week treatment with proton-pump inhibitors, most patient reported improvement and symptoms resolved in 61%. [69]

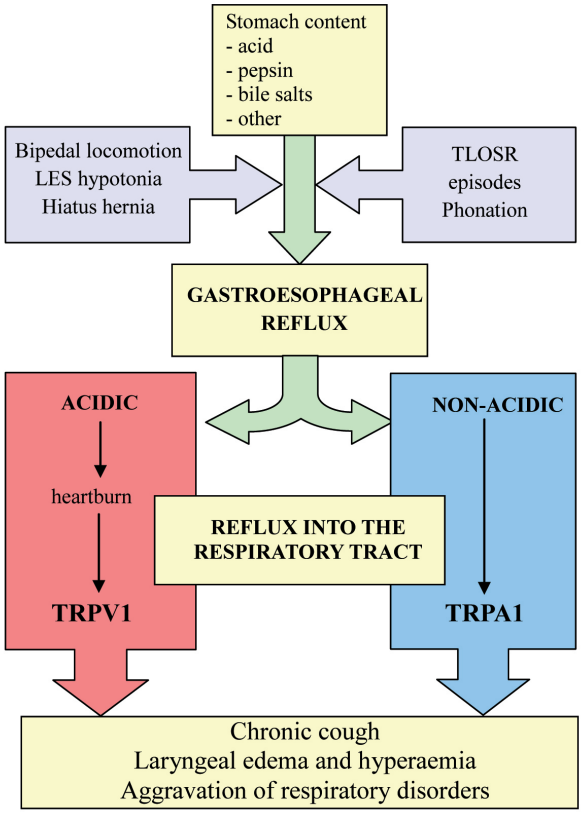

Fig. 1. Proposed mechanism of reflux into the respiratory tract. [60]

Another atypical symptom of GERD is laryngospasm, defined as a strong sudden abduction of vocal folds resulting in closure of the rima glottidis (so-called paroxysmal laryngospasm). It is a part of vagus nerve reflex, which is also conducted via the superior laryngeal nerve in response to irritating agents, such as acidic reflux contents. Stimulation of laryngeal chemoreceptors with pH < 2.5 results in reflex laryngospasm. This phenomenon presents clinically with dyspnea or apnea and aphonia. The research confirms the contribution of GERD to the development of the pathology and the success of treatment with proton-pump inhibitors. [13,18,54,55,68,82]

Various signs of LPR can be observed on laryngoscopic examination. The classic signs described in the literature include: edema and hyperaemia of the arythenoid and interarytenoid regions as well as posterior 1/3 of vocal folds; hypertrophy of the posterior commissure, sometimes pachydermia (thickening of the interarytenoid region, often with hyperkeratosis) – i.e. so-called inflammation of the posterior part of the larynx; also obliteration of the laryngeal vestibule (ventricles), subglottic edema (pseudosulcus), subglottic stenosis, less commonly paradoxical vocal fold movement, ulceration, vocal fold nodules, granuloma, Reinke's edema and even leukoplakia and cancer – which emphasizes the important role of laryngoscopy in assessing patients suspected of LPR. [14,18,40,61,64,68] Presence of thick mucus is often observed.

The association of LPR with laryngeal cancer can be explained by inflammation caused by irritation to the mucous membrane with consequent activation of neutrophils and accumulation of free radicals, which may contribute to cancerogenesis. [17]

Contact ulcer is a loss of mucous membrane of the vocal process or posterior commissure. With time, granulation tissue starts to form at the edges, and from this point, the lesion is called contact granuloma. The name is derived from a previous conviction that such lesions are caused by excessive abduction of the arytenoid cartilages during phonation. Although the mucoperichondrium covering the vocal process can be damaged during low-pitched phonation, cough and throat clearing, such lesions are rarely observed in individuals working with their voice, and also voice training and recurrent

excision of the lesion have low efficacy. It has been observed that in treatment-resistant cases, antireflux therapy is effective and can lead to total loss of symptoms, which confirms its association with LPR. [58]

Pseudosulcus vocalis, also referred to as subglottic edema, is the edema of the ventral surface of the vocal folds, extending from the anterior commissure to the posterior part of the larynx. Recognizing this sign is not sufficient to make a diagnosis of LPR, however, if it occurs in connection with other signs and symptoms of LPR, the probability of reflux reaches even 70%. [61,64]

Laryngoscopic signs in patients with LPR can be subtle or even missing. For this reason, the lack of laryngoscopic signs cannot constitute grounds for exclusion of LPR. [64,97]

On the other hand, the above-mentioned signs may be present in other disorders. In the study by Vavrick et al. [93], the specificity of the laryngoscopic signs attributed to reflux were investigated and no difference in occurrence of the signs was observed between patients with LPR and control group. The only noticeable difference was "cobblestoning" of the back wall of the throat. Similarly, Hicks et al. [32] reported that laryngoscopic signs commonly assigned to LPR were found in 86% of healthy volunteers. It does not prove the lack of usefulness of laryngoscopy in diagnosis of LPR, nevertheless it should be kept in mind that the assessment of this examination is subjective. [97]

Difficulties diagnosing LPR arise from the fact that symptoms and signs of the disease are not sufficiently sensitive (30-76%) or specific (55%) in order to confirm the diagnosis and exclude other causative factors. The research shows weak correlation between symptoms of LPR, laryngoscopic image and pH monitoring results. Much attention has been paid to develop a simple, cheap and non-invasive method of diagnosing LPR. [14,47,64]

Belafsky et al. developed two clinical scales to assess severity of LPR: Reflux Symptom Index (RSI) and Reflux Finding Score (RFS). The authors stated that those scales are a repeatable and simple method of diagnosing LPR, and the amount of time required to determine each score is 1 minute. According to the authors, both scales are a valuable tool for monitoring treatment outcomes in patients with LPR. [8,9,14,64]

RSI is a questionnaire assessing nine symptoms of reflux on scale from 0 (normal) to 5 (severe), thus the maximal score (suggesting the maximal severity of symptoms) is 45 points (Table 4). Scores above 13 points are considered abnormal. Considerably higher RSI scores were observed in patients with untreated LPR than in control group. [9,14,64]

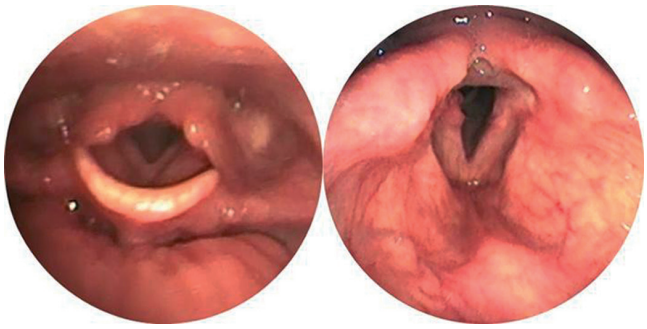

Fig. 2. Shows a sample image of the larynx in course of reflux disease

RFS assesses 8 types of lesion on laryngoscopic examination. It is estimated that RFS score higher than 7 denotes more than 95% probability of LPR. The range of scores is 0 to 26 points (the greatest severity of laryngoscopic signs) (Table 5). [8,64]

The studies conducted thus far show lack of consistency regarding specificity, sensitivity and test-retest reliability of RSI and RFS. [8,9,54,63,81]

Other indices for assessment of LPR have been developed, however, they are not widely introduced.

Domeracka et al. [23] developed a scale for assessment of endoscopically visualized lesions associated with reflux called "Warsaw A-E scale" (Table 6). The authors demonstrated correlation of this scale with RFS.

Leone and Mosca [54] proposed videolaryngoscopic staging classification of LPR, based on topographic criteria (discriminating between anterior and lateroposterior lesions) as well as anatomopathologial criteria (designating greater advancement to granulation tissue and ulceration, compared to erythema and edema). The anterior part of the larynx was defined as anterior 2/3 of the aryepiglottic folds, anterior 2/3 of the vocal folds and the epiglottis. The posterior and/or lateral part included: posterior 1/3 of the aryepiglottic folds, posterior 1/3 of the vocal folds, the arytenoid cartilages, interarytenoid region, piriform sinuses. Four stages (A, B, C, D) of laryngoscopic lesions were proposed (Table 7).

Witt et al. [96] proposed a method of color and texture analysis of the laryngoscopic image using an artificial neural network. The accordance with RFS, including both parameters, was 80.5%.

No single "gold standard" test for diagnosing LPR has yet been developed.

Diagnostic tools traditionally used in diagnosis of GERD such as barium swallow x-ray, esophageal endoscopy and 24-hour pH monitoring have insufficient sensitivity and specificity

Tab. IV. Reflux symptom index (RSI) [9,14]

SYMPTOMS WITHIN THE LAST MONTH	0 =NO PROBLEM 5 = SEVERE PROBLEM					
1. Hoarseness or a problem with your voice	0	1	2	3	4	5
2. Clearing your throat	0	1	2	3	4	5
3. Excess throat mucous or postnasal drip	0	1	2	3	4	5
4. Difficulty swallowing food, liquids or pills	0	1	2	3	4	5
5. Coughing after you ate or after lying down	0	1	2	3	4	5
6. Breathing difficulties or choking episodes	0	1	2	3	4	5
7. Troublesome or annoying cough	0	1	2	3	4	5
8. Sensations or something sticking in your throat or a lump in your throat	0	1	2	3	4	5
9. Heart burn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5
Total						

for diagnosing LPR. It is due to the fact that in most patients with LPR, esophagitis is not observed, because the esophageal mucosa is more resistant to acid and pepsin than the mucous membrane of the larynx and pharynx. For this reason, relying on standard diagnostic protocols for GERD can mislead an otolaryngologist into making a wrong diagnosis. [97]

Usually, the diagnosis of LPR is based on clinical presentation (from thoroughly taken history) and laryngoscopic examination, and then empirical therapy with double-dose proton-pump inhibitor, usually twice a day for 3 months (omeprazole test). [14,18,47,60,64,97] The resolution of symptoms with proton-pump therapy is considered diagnostic in LPR, however, some studies suggest that such approach may be unreliable even in patients with classic symptoms of GERD. [18,60] The sensitivity and specificity of the method in diagnosing GERD is estimated to be 78% and 54% respectively. [47] Lack of response to IPP therapy is considered a sign of wrong diagnosis or dosage. In those patients, further investigation should be conducted as described below. [18]

Further investigation is usually advised in patients with alarm symptoms (such as dysphagia, loss of weight, bleeding), qualified for fundoplication surgery and ones with long-standing GERD (in order to exclude Barrett's esophagus). [91,97]

24-hour esophageal pH monitoring is the only method that can objectively demonstrate presence of acidic contents in the distal part of the esophagus. [18] The sensitivity of the method in diagnosing atypical GERD is limited, thus a negative result does not exclude the diagnosis. Moreover, a positive result does not prove that GERD is responsible for the atypical symptoms. [91]

Dual-probe 24-hour pH monitoring is a more reliable tool and it is characterized by higher sensitivity and specificity in diagnosing LPR. The distal probe is placed 5cm above the LES and the proximal probe is located just above the UES. [47,64,97] An episode of LPR is defined as a decrease in pH < 4 around the proximal probe during or shortly after a reflux episode in the distal part of the esophagus, and the diagnosis is confirmed by measuring exposure time expressed in terms of reflux index. Reflux Index (RI) is defined as a percentage of time in which pH was below 4. [14] There are discrepancies in the literature as to pH criteria of GERD diagnosis – sample criteria are shown in Table 8.

Even dual-probe pH monitoring may not detect all cases of reflux due to phenomenon of non-acidic reflux. [60,68,79,90]

Another diagnostic method is multichannel intraluminal impedance (MII) measurement in the esophagus, which allows to detect non-acidic both fluid and gaseous reflux, thus increasing the sensitivity of diagnosing atypical GERD. [60,91] Using this method, a reflux episode is identified when the impedance decreases below 50% of the base value and this drop advances proximally. The combined use of impedance and pH monitoring allows to divide reflux into acidic (pH <4), slightly acidic (Ph 7-4) and slightly alkaline (decrease in impedance, pH ≥ 7). [79]

Esophagoscopy is primarily performed to exclude complications of GERD and other diseases. The indications for endoscopic examination in patients with LPR include: concurrent typical symptoms of GERD, long-term antireflux therapy, other risk factors of esophageal disorders – e.g. Barrett's esophagus, chronic cough. [47,97] This method is characterized by very high specificity in diagnosis of GERD-related esophagitis. Cobblestoning can typically be observed following chemical damage to the esophageal mucosa. [11] However, this sign is rarely present in patients with atypical GERD. Its prevalence

in such cases is estimated to be 10-30%, compared to 50% of patients with typical symptoms of GERD. [91]

On the other hand, Reavis et al. [72] in a study on patients with diagnosed esophageal adenocarcinoma (EAD) reported that those patients more frequently presented LPR symptoms (54%) than typical GERD symptoms (43%), although patients with Barrett's esophagus complained about typical symptoms (66%) rather than atypical (40%). For this reason, the authors consider it advisable to perform esophageal endoscopy in all patients with LPR. In that study, LPR symptoms included: chronic cough, asthma, aspirations, hoarseness, globus sensation, sore throat and sinusitis. The authors established that chronic cough was an independent risk factor of esophageal cancer, the symptom being present in 38.1% of patients with EAC.

Modification of lifestyle, pharmacotherapy and surgical methods are all used in management of LPR.

Lifestyle modifications should include: lifting the head of the bed, body mass reduction, avoidance of large meals, fats, citrus, mint, tomatoes, chocolate, caffeine, alcohol, carbonated drinks, cessation of smoking, avoiding medications lowering the LES tone, such as calcium channel blockers, anticholinergic agents, β2 adrenergic agonists, methylxanthines, but also avoiding supine position and eating meals at least 3h before sleep. These methods are effective in classic GERD. In case of LPR without typical GERD symptoms, their efficacy is limited, because laryngopharyngeal reflux usually occurs in a standing position during the day. [14,60,97]

In infants, it is advisable to introduce thickened hypoallergenic feed given frequently but in small portions at one time and to place the infant on the left side or with the head higher while sleeping. [11,94]

The most important and commonly used method of treatment, in both typical and atypical form of GERD, is pharmacotherapy with proton-pump inhibitors (PPI) that inhibit

Tab. V. Reflux Finding Score (RFS) [8, 14]

SYMPTOM	POINTS
Subglottic edema	0 = missing
	2 = present
Obstruction of vestibule / ventricles	[0 = missing]*
	2 = partial
	4 = total
Erythema / hyperemia of mucosa	[0 = missing]*
	2 = only surrounding arytenoid cartilages
	4 = diffuse
Vocal fold edema	[0 = missing]*
	1 = mild
	2 = moderate
	3 = severe
	4 = polipoid
Diffuse laryngeal edema	[0 = missing]*
	1 = mild
	2 = moderate
	3 = severe
	4 = constrictive
Mucosal hypertrophy of posterior commissure	[0 = missing]*
	1 = mild
	2 = moderate
	3 = severe
	4 = constrictive
Granuloma/granulation	0 = missing
	2 = present
Thick mucus in larynx	0 = missing
	2 = present
Total	

* Scores, which were not included in the publication of the authors of this classification, were added in brackets in order to make the range of the scale 0-26 points.

Tab. VI. Warsaw A-E scale describing lesions in the larynx and lower pharynx in course of GERD [23]

TYPE OF PATHOLOGY	FORM	DESCRIPTION OF PATHOLOGICAL FINDINGS
A	posterior laryngitis	inflammation of mucosa of posterior commissure and posterior parts of vocal folds (callus and ulceration)
B	annular	type A plus inflammation of mucosa of arytenoid and interarytenoid regions
C	saddle	type A or B plus inflammation and thickening of retroarytenoid region, vestibular folds and aryepiglottic folds
D	pseudotumor	type A or B or C and inflammation and thickening of lower pharyngeal mucosa
E	mixed	type A or B or C or D and subglottic edema or impaired mobility of cricoarytenoid joints or contact granulomas, or hypertrophy of vocal folds

H+/K+-ATPase found in parietal cells of the stomach. IPP do not only prevent direct exposure of the mucosa to acid, but also they can reduce to a certain degree damaged caused by pepsin, which becomes activated in acidic environment. [14] This group of drugs has strong and long-standing inhibitory effect on acid secretion in the stomach with few side effects. Currently, it is usually advised to use proton-pump inhibitors twice a day, a dose of 40mg of omeprazole or an equivalent in case of other PPIs, 30-60 minutes before a meal, for at least 3-4 months. Owing to the fact that the mucous membrane of the larynx and pharynx lacks defense mechanisms, even a small amount of acid can trigger symptoms. For this reason, stronger and longer suppression of acid production is required in managing LPR. Although the severity of symptoms decreases after about 3 months, complete resolution of symptoms and laryngoscopic signs takes about 6 months. Based on this, most authors suggest longer treatment ranging from 6 months to one year. [14,64,97]

The literature lacks accordance as to efficacy of PPI in treatment of LPR.

Kandogan et al. [40] conducted a study on a group of 9 patients assessing the impact of omeprazole therapy on the quality of voice in hyperfunctional dysphonia with laryngopharyngeal reflux. The patients were administered 20mg of omeprazole twice a day for 6 months. After treatment with omeprazole, improvement in voice quality parameters was observed. In a study by Shin et al. [81] conducted on patients with LPR, a significant improvement (over 50%) in assessment with RSI and RFS scales (75% and 57% respectively) was noted after 12-week administration of rabeprazole, regardless of the initial RSI and RFS values before treatment. The authors stated that RSI and RFS are not predictive factors of the response to PPI therapy in patients with LPR. [81] In the study by Patigaroo et al. [64], a significant improvement was observed in both intensity of symptoms (measured by RSI) after 8-week PPI therapy and intensity of laryngoscopic signs (measured by RFS) after 16 weeks of treatment. On the other hand, Steward et al. [86] did not observe any significant decrease in intensity of symptoms and laryngoscopic signs between patients who had received a 2-month therapy with rabeprazole and the control group.

Lack of response to treatment can be caused by many factors, including too low doses of PPIs, non-acidic reflux, wrong diagnosis of GERD. In such cases, as mentioned previously, it is advisable to exclude other causes of the symptoms and to perform further investigations, e.g. 24-hour pH monitoring; esophageal impedance monitoring may also be performed. Depending on the results, addition of drugs with other mechanism of action may be considered. [18,91]

Tab. VII. Laryngoscopic sign advancement stages, according to Leone and Mosca [54]

STAGE	LOCATION AND MORPHOLOGY OF LESIONS
A	erythema (hyperaemia) / edema posterior and/or lateral portion
B	erythema (hyperaemia) / edema posterior and/or lateral and aterior portion
C	ulceration/granulation posterior and/or lateral portion
D	ulceration/granulation posterior and/or lateral and aterior portion

Tab. VIII. pH monitoring criteria for diagnosing reflux [37,47]

	DISTAL PROBE	PROXIMAL PROBE
Total time	≥ 4.2%*	≥ 1%*
Standing position	≥ 6.3%*	≥ 1.3%*
Supine position	≥ 1.2%*	≥ 0.2%*
Number of reflux episodes during study (24h)	≥ 45 or ≥ 50**	≥ 1 (each)

* percentage of time, in which pH < 4; ** - depending on source

Histamine H2 receptor antagonists (H2 blockers) reduce the production of acid in the stomach, however, their efficacy is limited due to the fact that they do not influence gastrin production and do not act on acetylcholine receptors. Although these drugs suppress acid production, the failure rate of their addition to standard therapy is still significant and accounts to 10-17%, depending on the study. [11,14] Antacids containing alginic acid react with the stomach acid forming gel and lower pH in the stomach, and therefore they protect the mucous membrane not only by inhibiting pepsin activation, but also by creating a physical barrier from the reflux contents..." str. 35 - akapit 5 - "...Baclofen, a GABA analogue that is widely used in managing neuromuscular disorders, significantly reduces the number of TLOSR episodes, its use being limited due to considerable side effects. Mechanoreceptors of the LES, dependent on the vagus nerve, can be inhibited by gamma-aminobutyric acid (GABA) B-type receptor agonists. Baclofen, a widely used GABA analogue in managing neuromuscular disorders, significantly reduces the number of TLOSR episodes, its use being limited due to considerable side effects. Molyneux et al. Report use of low-dose baclofen in treatment of LPR. [60]

Because increase in motility and prevention of delayed emptying of the stomach lower the risk for reflux, it is sometimes proposed to use prokinetic agents such as metoclopramide, domperidone and macrolide antibiotics for treatment of LPR. Poe and Kallay [67] reported improvement in patients with GERD-related cough, who had not responded to monotherapy with PPIs, following addition of metoclopramide or cisapride.

However, it should be emphasized that cisapride has significant side effect, namely QT prolongation. Domperidone and metoclopramide are used at a standard dose of 10mg 3 times a day. It is worth noting that domperidone does not evoke extrapyramidal side effects, which are possible for metoclopramide. [60] Low-dose erythromycin (2x250mg) is widely used as a prokinetic agent. [60] In the study by Mertens et al [57], introduction of a newer macrolide, azithromycin, reduced the frequency of reflux episodes, exposure time of the esophageal mucosa to acid and the concentration of bile acids in bronchoalveolar lavage fluid in patients who had undergone lung transplantation.

Molyneux et al. [60] recommend trying each of the drugs listed above for 4 weeks in case of no response to previous PPI therapy, as long as initial doses of those drugs are well-tolerated.

For *Helicobacter pylori* infection, the first-line treatment is usually the so-called triple therapy, i.e. standard-dose PPI 2 times a day along with amoxicillin 2x1g and metronidazole 2x500mg for 10 days. Polish guidelines regarding pharmacotherapy of *H. pylori* eradication are summarized in Table 9. Currently, clarithromycin should not be first-line choice due to developing resistance of *H. pylori* to the antibiotic. After two failures to eradicate, antibiogram should be obtained. Some studies indicate possibility for adding probiotic to the triple therapy. [6,75]

In the literature, successful surgical treatment of patients with severe or life-threatening LPR has been described. The most commonly performed procedure is Nissen fundoplication, nowadays usually laparoscopic. In this procedure, the fundus of the stomach is wrapped around the distal part of the esophagus in order to create a barrier for reflux. This method can be effective in patients who do not respond to PPI therapy, when there is a possibility of non-acidic reflux. [97] In the study by Dallemagne et al. [20], no significant symptoms of GERD were observed in 93% of patients 5 years after fundoplication surgery, and in 89.5% 10 years postoperatively. Hunter et al. [34] reported complete resolution or reduction in severity of respiratory symptoms in 87% of patients with GERD.

It is believed, however, that the effectiveness of antireflux surgery in atypical GERD is lower and less predictable than in typical GERD, and this information should always be communicated to the patient before the intervention. [14] According to some studies, surgical treatment is usually ineffective in patients showing resistance to PPI therapy. [18]

Swoger et al [87] reported no benefits of antireflux surgery in patients with laryngeal symptoms of GERD.

In the study by So et al. [83], resolution of Heartburn was observed in 93% of patients, while atypical GERD symptoms resolved only in 57%, and the most important predictive factor for successful treatment was the preoperative response to pharmacotherapy. [91]

Endoscopic procedures are an alternative method of treatment, and these include: Strett method, in which radio frequency wave energy directed onto the LES and subcardial region, biopolymer implantation method surrounding the LES and gastroplication, in which mucosal sutures are made just below the Z line. [74] However, although all three methods subside severity symptoms and use of PPI, none of the methods improves the pH monitoring results significantly. [77]

Poelmans et al. [68] summarized the rules of managing atypical GERD into an algorithm. (Figure 3)

According to this algorithm, if reflux is suspected based on clinical presentation, double-dose PPI should be used for at least 3 months as a first-line treatment. Higher doses and longer time of therapy are motivated by the previously mentioned facts. In case of failure of such treatment, 24-hour pH monitoring is performed while still on PPI. This recommendation is based mainly on observations of typical GERD, when acidic reflux is detected on pH monitoring in half of the patients, who present symptoms and esophagitis despite appropriate treatment. However, the data confirming such phenomenon in atypical GERD is limited. [68]

Poelmans et al. [68]established that pH monitoring performed during PPI therapy is rarely positive, and thus does not exclude persisting reflux as a cause of the symptoms. Higher sensitivity might be accomplished by esophageal impedance monitoring, but this method is expensive and poorly accessible, and therefore it may be beneficial to monitor pH after termination of PPI therapy. Furthermore, the authors stated that the role of endoscopy is underestimated and the prevalence of esophagitis associated with atypical GERD is higher than previously estimated. [68]

For this reason, Poelmans et al. proposed a new algorithm shown in Fig.4.

The authors stated that the data in the literature regarding the efficacy of prolonged double-dose PPIS therapy are insufficient to incorporate such approach, if the diagnosis of GERD is not confirmed. Therefore, they recommend trying standard-dose PPI therapy for 6 -8 weeks initially. If this proves to be ineffective, the authors recommend to continue PPI therapy at the lowest effective dose, as long as any treatment is still necessary, and to per-

form an endoscopic examination, optimally 4 weeks following discontinuation of the therapy. They also recommend 24-hour pH monitoring, emphasizing that impedance monitoring may be included in the algorithm in the future. According to the authors, if the pH monitoring results are normal, other causes of the symptoms should be considered, and in case of abnormal results – PPI should be administered at a higher dose for at least 3 months. Surgical treatment can be considered in patients who require prolonged PPI therapy or do not respond to treatment and there is convincing evidence for association of symptoms with reflux. [68]

Another approach was proposed by Postma et al. [71] The authors distinguished three categories of LPR: *minor, major* and life-threatening, based on severity of symptoms and their impact of patient's functioning, and they adjusted treatment to intensity of the disease. In *minor* type, symptoms are troublesome but do not negatively affect work and social life of the patient. The most common symptoms in this group of patients include: recurrent dysphonia, throat clearing, globus sensation, dysphagia, as well as mucosal edema and inflammation of the posterior part of the larynx on laryngoscopic examination. The initial choice of treatment can vary in this type, but the authors suggest that less aggressive therapy should be considered. They recommend diet and lifestyle modification (e.g. cessation of smoking, reduction of alcohol intake), however, they do not see raising the head of the bed as indicated, unless pH monitoring reveals significant reflux in supine position at night. The authors recommend use of H2 blockers or antacids, and in case of their ineffectiveness – PPIs 2 times a day initially, and later depending on symptoms. If the therapy is ineffective, the authors perform pH monitoring and modify the dose or type of PPI based on the results, or qualify the patient for fundoplication in more severe cases. The PPI therapy is continued for 6 months. Then, reduction of dosage or cessation of treatment is considered, but only after having informed the patient about the possibility of symptom recurrence. Some patients require life-long therapy with PPIs. In *major* type, the symptoms affect work and social life of patients. In this group of patients, the authors recommend initiating therapy with diet and lifestyle modification and use of PPIs 2 times a day. If there is no improvement after 2 months, doubling of PPI dose or addition of an evening dose of H2 receptor antagonist is considered, depending on the daily reflux pattern. If still no improvement is noticed after another 2 months, pH monitoring is performed with following PPI regime modification or fundoplication. If no symptoms are observed on two consecutive visits at two-month intervals, the dose of PPI is gradually reduced, the PPI is substituted for H2 blocker, or therapy is ceased. However, if the symptoms recur, the dose of PPI is gradually increased. The *life-threatening* type is characterized by obstruction of respiratory tract, including glottis or subglottic stenosis, glottis web, laryngospasm, severe paradoxical vocal fold movement, asthma, dysplasia and laryngeal cancer. This type requires intensive antireflux treatment. The authors usually initiate therapy with PPI 3-4 times a day. They recommend pH monitoring with esophageal monitoring study, optimally before starting therapy, which is sometimes impossible to do due to the need for an immediate life-saving surgical intervention. Those patients, especially young ones, are often qualified for fundoplication. [71]

When managing LPR, it should be remembered that no significant advantage of any single algorithm over others has been proven. Further research is required in order to develop reliable guidelines for managing atypical GERD.

5. OTHER CONDITIONS RELATED TO GERD

5.1 Chronic rhinosinusitis

GERD may also play part in the pathogenesis of chronic rhinosinusitis (CRS).

Lin et al. [52] reported that the prevalence of CRS in the course of GERD is 2.36 times higher than in control group, while CRS without polyps occurred more often that CRS with nasal polyps. Loehrl et al. [53] found that 95% of patients with recurrences of CRS after pharmacological and surgical treatment had abnormal pH results in the pharynx, and 47% in the esophagus. In nasal lavage fluid of all examined patients with CRS, the presence of pepsin was revealed, compared to lack of it in the control group. This may indicate a significant role of irritation of the nasal mucosa by reflux contents in the pathophysiology of CRS, which leads to inflammation, and subsequently impairs the mobility epithelial cilia, while on the other hand, it leads to edema and obstruction of the ostiomeatal complex. Another possible mechanism is the vagus nerve reflex, leading to edema of the nasal mucosa and increases secretion of fluid. In the next possible mechanism, GERD-induced eosinophilic esophagitis would cause overexpression of a proinflammatory mediators such as thymic stromal lymphopoietin (TSLP), which is significant in pathogenesis of CRS. [52,17] On the other hand, Flook and Kumar [29], based on Medline and EMBASE databases analysis, stated that the literature data is insufficient to assume GERD as a significant causative factor of CRS and to consider antireflux therapy in managing CRS.

5.2. Otitis media

Connection between GERD and otitis media is still undetermined.

Two studies on children with otitis media with effusion revealed higher concentration of pepsinogen/pepsin in the effusion of the middle ear than in the blood serum, which indicates a role of reflux in pathogenesis of this disease. [28, 88]. Probably, similarly to inflammatory changes of the nasal mucosa in course of CRS, the inflammation of the nasopharyngeal mucosa impairs mobility of the cilia and causes edema with following obstruction of the pharyngeal opening of the auditory tube and disfunction of the auditory tube. [17] In the study by Poelmans et al. [69] conducted on 5 adult patients with chronic suppurative otitis media, GERD was found in all patients, and resolution of symptoms was seen in all patients after administration of proton-pump inhibitors.

5.3. Dental cavities (erosion)

Probably, similarly to inflammatory changes of the nasal mucosa in course of CRS, the inflammation of the nasopharyngeal mucosa impairs mobility of the cilia and causes edema with following obstruction of the pharyngeal opening of the auditory tube and disfunction of the auditory tube. [17] In the study by Poelmans et al. [69] conducted on 5 adult patients with chronic suppurative otitis media, GERD was found in all patients, and resolution of symptoms was seen in all patients after administration of proton-pump inhibitors.

Pathogenesis of dental erosions in GERD is based on dissolution of the inorganic component of enamel, i.e. hydroxyapatite crystals, which occurs when pH is lower than 5.5. [62, 95]

Those changes predispose to attrition (pathological wear of occlusal surface of teeth due to their mutual contact) and abrasion (tooth wear caused by hard objects or abrasives), which can lead to loss of teeth, cosmetic defects and even change of the facial appearance. [33,62,95]

5.4 Chronic cough

Chronic cough is defined as a persistence of cough for more than 8 weeks. GERD is considered to constitute one of three main causes of chronic cough, along with post-nasal drip and asthma, and it is responsible for 20% of cases of this symptom. [35,68,90,91] GERD should be suspected especially in patients who do not show signs of other possible causes of chronic cough, involving cough-inducing drugs (e.g. ACEI), smoking, exposure to other environmental irritating factors, asthma, chronic bronchitis, post-nasal drip, normal chest x-ray. GERD-related cough usually occurs during daytime, in a standing position and is non-productive. [90,91] Pathophysiology of this symptom in GERD has been described above.

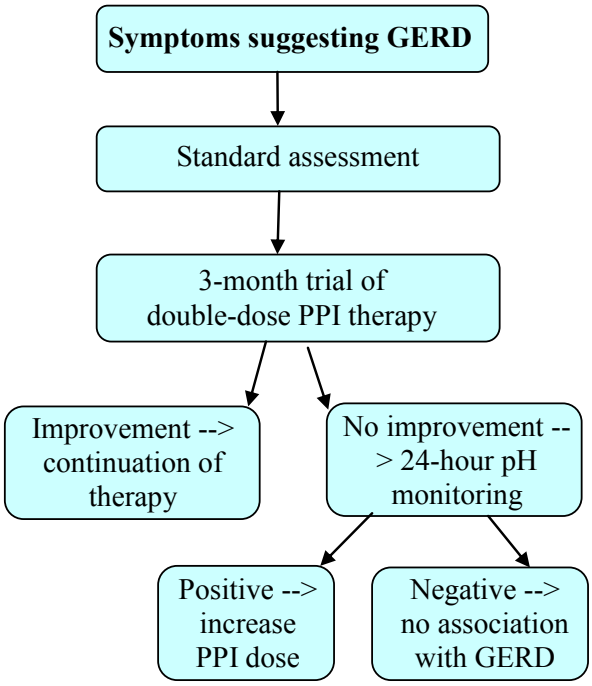

Fig. 3. Classic algorithm of managing extraesophageal symptoms of GERD, according to Poelmans et al. [68]

Similarly as in reflux laryngitis, diagnostic methods used in typical GERD are less helpful in diagnosing GERD-related cough. Typical symptoms of GERD, such as Heartburn and regurgitation, are present in 25% of patients. [68,90] Usually, esophagitis is not visible, and thus esophageal endoscopy has limited diagnostic value in this instance, however, the examination is justified as this group of patients is at higher risk for developing esophageal adenocarcinoma.

Sifrim et al. [79] proposed combined use of impedance, pH and motility monitoring in diagnosing GERD-related cough. Esophageal motility study conducted with simultaneous pH and impedance monitoring allows to determine the presence of cough and its relation to reflux episodes. It is noteworthy that simple coincidence is not sufficient, because cough may not only be caused by GERD, but also, as mentioned above, it may evoke a reflux episode itself. Establishing whether cough is the cause or the result of reflux is crucial for the choice of appropriate treatment. [79] In that study, the correlation between cough and a reflux episode was recognized when the time interval between those two phenomena did not exceed 2 minutes. The authors made a distinction between GER-induced cough (i.e. occurring within 2 minutes after an episode of reflux) and GER-preceding cough (i.e. present within 2 minutes before a reflux episode). It

was found that 30.6% of cough episodes were associated with GER, half of which were triggered by the reflux, either acidic (65%), slightly acidic (29%) or slightly alkaline (6%). [79]

Treatment of GERD-related cough is still controversial. The most common choice is, like in reflux laryngitis, empirical therapy with double-dose proton-pump inhibitors for at least 3 months. [90]

Kiljander et al. [44] reported significant reduction of symptoms in patients with GERD-related cough who were given 40mg of omeprazole daily for 9 weeks, compared to control group who received placebo. Moreover, the improvement lasted even after therapy termination. It should be noted, however, that only patients with acidic reflux were studied, because a drop of pH below 4 in the esophagus was accepted as a diagnostic criterion for GERD.

Chang et al. [16] stated, having analyzed the Cochrane database, that there is no clear proof for effectiveness of PPI therapy in managing GERD-related cough.

Furthermore, Reiche et al. [73] reported a case of omeprazole-induced cough, and therefore it should be remembered that cough may appear or worsen during PPI therapy. In the study by Baldi et al. [5], the best predictive factor of efficacy of standard proton-pump therapy was improvement after 4-week trial of PPI therapy, but esophageal endoscopy and pH monitoring did not show statistically significant predictive value. [5]

In patients who do not respond to PPI, other causes of cough should be considered, including non-acidic reflux. [90] In this group of patients, it may be appropriate to reduce number of reflux episodes during transient LES relaxations, which can be achieved by pharmacotherapy with baclofen or antireflux surgery. [79]

Allen and Alvari [1] reported effectiveness of laparoscopic Nissen fundoplication in managing GERD-related cough. After surgical intervention, the cough resolved in 51% of patients and a noticeable reduction in severity was observed in 31%. [90]

5.5 Asthma

Asthma is a heterogeneous disease and only a portion of adult patients presents history of typical atopic phenotype in their childhood. Chronic cough can be the only symptom of cough-variant asthma and final diagnosis depends on response to antiasthmatic treatment. [60]

The literature describes association between asthma and gastroesophageal reflux disease, while GERD and/or esophagitis is diagnosed in 30-80% of asthmatic patients. [18]

A significant correlation between GERD and asthma is confirmed by the analysis of Medline and EMBASE databases conducted by Havemann et al. [30]. That study shows that average prevalence of GERD symptoms in asthmatic patients is 59.2% compared to 38.1% in control group. Abnormal results of pH monitoring were found in 50.9% of asthmatic patients, esophagitis in 37.3% and hiatus hernia was diagnosed in 51.2%. Average prevalence of asthma in GERD patients was 4.6%, compared to 3.9% in control group.

Exacerbation of asthma symptoms after meals, alcohol consumption, at night and in supine position, adult-onset asthma, ineffectiveness of antiasthmatic drugs and history of GERD symptoms prior to onset of asthma, should raise suspicion of GERD-related asthma. [90, 91]

Causes of association between asthma and GERD have not been fully explained. [18]. The role of microaspiration of reflux contents into the airways, as well as the indirect reflex mechanism - as described above – has been emphasized in the pathogenesis of GERD-related asthma. It is believed that GERD and microaspirations can contribute to inflammation of the respiratory tract and intensification of allergic asthma. Exacerbation of asthma symptoms can cause inspiratory position of chest, more negative intrathoracic pressure, flattening of the diaphragm and shortening of abdominal portion of the esophagus, which can predispose to reflux. It leads to a 'vicious-circle' mechanism, wherein GERD intensifies asthma symptoms, which in turn leads to intensification of reflux. [60, 66]

In the study by Sontag et al. [85], more than 80% of asthmatic patients presented abnormal acidic reflux on 24-hour pH monitoring. In the study, reduction of lower esophageal sphincter (LES) pressure, prolonged exposure of the esophageal mucosa to acidic contents and delayed esophageal clearing in both standing and supine position, were all found in asthmatic patients. No significant difference in intensity of symptoms was found between patients receiving bronchodilators and those without such treatment, which indicates that LES hypotonia is not simply a side effect of antiasthmatic therapy. [85]

Jack et al. [36] described presence of reflux contents microaspirations into the trachea in asthmatic patients, accompanied by significant decrease in peak expiratory flow (PEF) during those episodes.

On the other hand, as mentioned previously, coughing attacks associated with asthma can facilitate overcoming of the LES barrier by reflux contents by means of negative intrathoracic pressure. This study also described a decrease in LES tone, which can predispose to reflux episodes, relating to antiasth-

matic drugs such as β2 adrenergic agonists [48], corticosteroids [49], and theophylline [10].

There is no consensus concerning efficacy of antireflux drugs, such as H2 blockers and proton-pump inhibitors in treatment of GERD-related asthma.

Field and Sutherland [27], in the analysis of Medline database, found that antireflux treatment in asthmatic patients decreases intensity of asthma symptoms and need for antiasthmatic drugs, however, it does not significantly affect lung function assessed using spirometry. Administration of proton-pump inhibitors may be particularly important in patients with nocturnal symptoms. Kiljander et al. [45] reported a decrease in nocturnal symptoms of asthma but no improvement of daytime symptoms in patients diagnosed with asthma and GERD, who were treated with 40mg of omeprazole daily for 8 weeks. Another study [43] showed improvement in PEF parameter following 16-week esomeprazole therapy of patients with GERD and nocturnal asthma symptoms, however, no improvement was observed in patients without GERD or nocturnal asthma symptoms.

On the other hand, in the analysis of Cochrane database conducted by Coughlam et al. [19], it was established that antireflux treatment did not cause any improvement in spirometric parameters, such as FEV1 (forced expiratory volume in 1 second) or PEF, nor asthma symptoms both during daytime and at night, nor need for the use of antiasthmatic drugs.

Similar results were obtained in the study conducted by the American Lung Association Asthma Clinical Research Centers [3] on patients with poorly controlled asthma. Following 24-week esomeprazole therapy, no improvement in control of asthma was noticed, regarding lung function parameters, reactivity of the airways, intensity of symptoms, nocturnal awakenings and quality of life, compared to control group. Also, no benefits were found in the subgroup of patients with GERD diagnosed by pH monitoring.

Also, there is no confirmation of the efficacy of antireflux surgeries in GERD-related asthma. Field et al. [28], based on Medline database analysis, showed that antireflux interventions can lead to a decrease in intensity of asthma symptoms and need for antiasthmatic drugs, but they have very little impact on lung function. The effectiveness of antireflux surgery and conservative treatment was similar.

Sontag et al. [84] reported no significant influence of antireflux interventions on lung function, need for antiasthmatic drugs and total survival of patients with both asthma and GERD. However, they observed a significant reduction of asthma symptoms in this group, compared to patients treated with ranitidine, and those from control group, where no improvement was found.

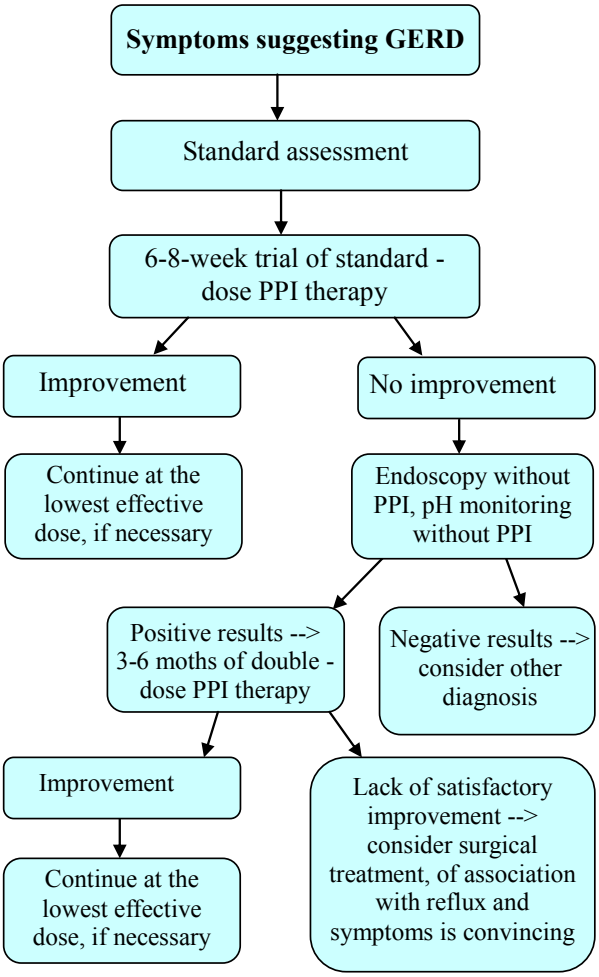

Fig. 4. New algorithm of managing extraesophageal symptoms of GERD, as proposed by Poelmans et al. [68]

It is now believed that empirical trial of proton-pump therapy should be administered for 2 or 3 months in patients with asthma and GERD, and then, therapy should be continued at the lowest effective dose that controls symptoms. In patients who do not respond to this therapy, esophageal impedance along with pH monitoring should be considered in order to determine the character of reflux, including non-acidic reflux. Determination of patient subgroups, who can benefit from both pharmacological and surgical antireflux treatment, requires further research. [90]

5.6. Chronic obstructive pulmonary disease (COPD)

Patients with COPD can be especially predisposed to gastroesophageal reflux disease due to considerable changes of intrathoracic pressure, frequent cough, flattening of the diaphragm, use of β2 adrenergic agonists, as well as changes in thorax anatomy observed in advanced stages of the disease. [42, 60]

Kempainen et al. [42] diagnosed GERD in 57% of patients with advanced COPD. Typical symptoms of GERD were not present in the majority of patients. Reflux into the proximal part of the esophagus was especially frequent, even with normal results of pH monitoring in the distal esophagus.

Eryuksel et al. [26] found symptoms of LPR in 44% of patients with COPD and reported alleviation of COPD symptoms in those patients following treatment with proton-pump inhibitors.

Exacerbations of COPD symptoms without inflammatory markers elevation are common. Identification of reflux as a reason of the complaints in a portion of those patients would have a significant influence on their treatment. [60]

5.7. Other disorders of the respiratory system

GERD is also more often diagnosed in other respiratory system diseases. Association of idiopathic pulmonary fibrosis (IPF) and GERD has been reported. Abnormal results of esophageal pH monitoring were found in 67-88% of patients with IPF. GERD in those patients is often asymptomatic. A probable pathomechanism of IPF in those instances is microaspirations of reflux contents. [31, 50] In patients who had undergone lung transplantation, microaspirations of reflux contents, both acidic and non-acidic, may contribute to development of bronchiolitis obliterans syndrome (BOS) and thus to transplant rejection. [12,21,24] D'Ovidio et al. [24] reported presence of bile acids in broncho-alveolar lavage fluid in patients with BOS.

6. CONCLUSIONS

LPR is a common problem in the otolaryngological practice, and its results may be very serious. Despite a large number of publications on this subject, there are still many controversies. Better understanding of the pathophysiology of this disease would allow to develop more effective approaches to its management." LPR is characterized by a significant diversity and a lack of specificity of symptoms, which makes it difficult to make a right diagnosis. Besides, there is a lack of clear evidence for reliability of tests used in diagnosis of this illness, like e.g. esophageal pH monitoring. Because of inconsistent results research thus far, algorithms of managing extraesophageal GERD symptoms seem to be still imperfect and require further modification. Because of that, the necessity for further research on LPR should be emphasized.

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