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Itopride in treatment of laryngopharyngeal symptoms of gastroesophageal reflux disease

Maria Janiak

Department and Clinic of Gastroenterology and Hepatology, Medical University of Gdansk, Poland; Head: prof. Krystian Adrych MD PhD

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ABSTRACT: In everyday otolaryngological and gastroenterological practice, the diagnosis and treatment of extraesophageal forms of gastroesophageal reflux disease are often challenging. It is sometimes the case that treatment ordered by other specialists proves ineffective or even worsens the symptoms. There is no golden standard of diagnosis for otolaryngological forms of GERD, and currently used tools (gastroscopy, laryngoscopy, impedance and pH testing) have low sensitivity and specificity. After finishing a course of successful treatment, the patients often come back to our offices with the very same symptoms. In order to improve the efficacy of treatment, a prokinetic agent can be added to the standard proton pump inhibitor therapy.

KEYWORDS: esophagolaryngeal reflux, gastroesophageal reflux disease, itopride

ABBREVIATIONS

BMI – body mass index
GERD – gastroesophageal reflux disease
LES – lower esophageal sphincter
LPRD – laryngopharyngeal reflux disease
MII-pH – multichannel intraluminal impedance and pH testing
PPI – proton pump inhibitors
RFS – reflux finding score
RSI – reflux symptom index

INTRODUCTION

The widespread occurrence of the gastroesophageal reflux disease (GERD) affecting over one billion people worldwide makes it one of the 'new millennium epidemic' diseases. Many forms and symptoms of GERD urge many patients to seek help among various specialists. In clinical practice, it is sometimes the case that the therapy ordered by other specialists (which can cause lower esophageal sphincter relaxation as a side effect) exacerbates the undiagnosed reflux. According to the Montreal definition, which has not changed for the past 15 years, there are accepted (reflux is an accepted cause of the symptoms) and possible (reflux is one of many factors leading to symptoms) extraesophageal forms of GERD, meaning that half of possible manifestations (4/8) require cooperation between otolaryngologists and gastroenterologists.

The diagnosis of GERD in patients presenting with laryngological symptoms is even more challenging since most of them do not develop typical reflux symptoms [1]. This can be explained by the fact that the stomach contents rise up above the lower esophageal sphincter (LES) to the esophagus only for a short period of time, which is not enough to irritate the mucous membrane and cause typical symptoms. The laryngeal apparatus is more prone to injury compared to the stratified squamous epithelium of the esophagus, due to the lack of the protection by saliva and intracellular mechanisms. GERD should be assumed an underlying condition in patients with asthma, chronic cough or laryngitis. In all such patients, other causes than GERD should be evaluated [2]. The laryngopharyngeal reflux is defined as upper respiratory inflammation caused by both direct and indirect reflux of the gastroduodenal contents [3].

PATHOPHYSIOLOGY

There is a number of theories regarding the pathophysiology of laryngeal abnormalities in GERD.

Reflux laryngitis can be caused by a direct injury by acid and pepsin. Pepsin remains active in the presence of hydrogen ions and pH lower than 6. The injury of the esophageal mucosa due to exposition to acid and/or pepsin are reversible, while it can be irreversible in the case of laryngeal mucosa. The laryngeal apparatus is more prone to damage by corrosive agents because it is not constantly covered with saliva and does not have intracellular protective mechanisms. Pepsin is considered more corrosive for the larynx than stomach acid. Serious laryngeal injury occurs in the presence of hydrogen ions (low pH 2.0–4.0) when pepsin is activated. The laryngeal apparatus is more prone to injury due to the lack of protection by saliva and intracellular mechanisms. In response to corrosive contents, the blood vessels of the laryngeal mucosa and submucosa dilate, followed by development of petechiae, interstitial edema, inflammation, fibroblast infiltration and fibrosis [4].

One pathophysiological theory assumes direct injury to the mucous membrane of the pharynx and larynx due to microaspiration of reflux contents rich in hydrochloric acid, pepsin and bile salts. In response to inflammation, the epithelium thickens and mucus becomes more dense, the vocal fold mucosa shows microscopic and macroscopic changes affecting voice emission and leading to grunting or even coughing [5].

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Tab. I. Global definition of GERD including forms with so-called laryngological mask.

ESOPHAGEAL SYMPTOMATIC SYNDROMES	ESOPHAGEAL SYNDROMES WITH ESOPHAGEAL INJURY	ACCEPTED EXTRAESOPHAGEAL SYMPTOMS	POSSIBLE EXTRAESOPHAGEAL SYNDROMES
Typical reflux	Reflux esophagitis	Reflux-related cough	**Pharyngitis**
Reflux-related chest pain	Reflux-related esophageal stenosis	**Reflux laryngitis**	**Sinusitis**
	Barrett's esophagus	Reflux asthma	Idiopathic pulmonary fibrosis
	Esophageal adenocarcinoma	Reflux dental erosions	**Recurrent otitis media**

Another interesting physiological aspect of otolaryngological forms of GERD is the presence of the proton pump (H/K-adenosine triphosphatase) in the glands of the laryngeal mucosa and the submandibular salivary gland, which affects acidity and thus activates pepsin [6].

The laryngeal mucosa does not provide protection against pepsin and low pH (lack of buffering saliva; no stratified squamous epithelium resistant to food contents of the esophagus; more vulnerability to changing pH). Cytoprotective mechanisms of the laryngeal mucosa include locally alkalizing carbonic anhydrase isoenzyme III, which inactivates pepsin.

The predominance of corrosive agents over protective factors leads to local laryngitis and cough, as well as other symptoms including hoarseness, globus sensation, vocal fatigue and grunting.

DIAGNOSIS OF OTOLARYNGOLOGICAL FORMS OF GASTROESOPHAGEAL REFLUX DISEASE

Establishing a correlation between laryngitis and reflux episodes can be clinically challenging. Clinical presentation of reflux laryngitis is non-specific. The spectrum of symptoms in patients with reflux laryngitis can vary widely. The patients most often complain about hoarseness, especially after night rest or on lying down, prolonged time to normal voice emission after waking up ('voice warm-up'), globus sensation, morning cough, grunting, post-nasal drip. Other characteristic symptoms include halitosis despite correct oral hygiene.

It is a known fact that lowering oral pH to 5.5 leads to enamel damage (dissolving of hydroxyapatite crystals causing erosions) on the palatal surface of the upper teeth, and on the occlusal and buccal surfaces of the lower teeth. Teeth damaged due to erosion are more transparent, more sensitive to thermal, mechanical and chemical stimuli. In the case of untreated reflux disease and prolonged exposure of the oral mucosa to low pH, mineral deposits form inside erosions and the exposed dentin becomes dark yellow, and the erosion leads to pulp exposure. It is even more probable that laryngeal symptoms are caused by reflux when the patient complains about xerostomia. This complain may be due to low pH reducing viscosity and elasticity of saliva; despite normal production at about pH 4, the gelous structure of saliva is broken, which affects its viscosity [7].

It can be difficult to determine whether gastroesophageal or laryngopharyngeal reflux is the underlying cause of pathology of the upper respiratory tract, larynx, paranasal sinuses or ears, due to the fact that all those abnormalities can occur without any symptoms of gastric reflux. Moreover, because the symptoms can vary and are non-specific, there is no golden standard of diagnosis. Currently used tools such as gastroscopy, laryngoscopy and pH testing have both low sensitivity and specificity in diagnosing LPRD (laryngopharyngeal reflux disease). For diagnosis of laryngopharyngeal forms of reflux disease, clinical questionnaires such as RSI (reflux symptom index) or pathological studies (RFS – reflux finding score) can be implemented.

However, reflux laryngitis should not be diagnosed solely based on laryngoscopy [8, 9]. Although the signs of laryngopharyngeal reflux are non-specific (inflammation of the posterior larynx, contact ulceration, subglottal narrowing [pseudosulcus], diffuse laryngeal odema and erythema, dulled interarytenoid region, narrowed laryngeal ventricles, vocal cord nodules, or even laryngeal cancer), it is advisable to perform laryngoscopy to exclude cancer. Interpretation of laryngological assessment varies with the operator, thus the diagnosis may be subjective and not very reliable [10, 11]. There is a known phenomenon of overdiagnosis of LPRD based on laryngoscopy, which may result in unnecessary treatment which proves ineffective.

Vaezi reported that morphological abnormalities on otolaryngological examination may occur in healthy individuals (interarytenoid obstruction: 71%; reddening of the medial surface of the arytenoid: 30%; cobblestone of the posterior wall of the throat: 21%; reddened interarytenoid obstruction: 15%; granulation of the medial arytenoid surface: 14%) [8]. Commonly performed laryngology results in overdiagnosis of reflux-associated abnormalities which entails unnecessary further diagnostic workup. According to Vaezi, it is not a mistake to suspect GERD as a possible etiology, but rather to insist on this diagnosis despite the lack of response to aggressive treatment [10].

It is not recommended to perform upper gastrointestinal endoscopy for further evaluation of GERD-related laryngitis [1]. It should be kept in mind that a lack of morphological abnormalities on esophageal endoscopy does not exclude GERD, since in more than half of GERD patients no macroscopic mucosal erosion are present. An indication for gastroscopy is the presence of alarming symptoms (weight loss, dysphagia, odynophagia, coffee-ground vomiting or melaena).

In patients with extraesophageal presentation but without typical GERD symptoms, reflux monitoring with esophageal impedance testing may be considered [1]. To verify the underlying cause of laryngeal pathology, multichannel intraluminal impedance and pH testing (MII-pH) can be implemented. Based on the results, both acidic and non-acidic reflux episodes can be detected as well as the extent of reflux, which is important for effective treatment. Symptomatic

I	Eat often (every 3 hours, 5–6 times a day) but in small portions.
II	After eating – do not lie down for at least 2 hours.
III	Do not eat late at night, especially when you experience heartburns or waking up at night.
IV	Raise the pillows by 10–15 cm, try lying down on the left side at night.
V	Try to eliminate fatty foods from your diet and replace it with protein-rich meals.
VI	Try reducing coffee drinking, quit smoking..
VII	Or your waist line increased by 3.5 cm – lose some weight.
VIII	Moderately increase your physical activity (marching, swimming, cycling) – but not excessively.
IX	Eliminate foods which in your opinion make your symptoms worse (e.g. citrus fruits, spicy meals, soda, alcoholic beverages).
X	Take medications according to your physician's recommendations, be careful about the time intervals (between medication intake and meals) which should be kept for each medication.

Remember, despite its chronic character, your condition is usually mild, and unnecessary and unjustified concern may delay full recovery.

Fig. 1. Lifestyle modifications according to the author.

chronic laryngitis can be due to mildly acidic reflux, and hence it is preferred to apply pH and impedance testing rather than pH testing only. The volume of reflux determines the extent of the exposure of the esophageal mucosa to irritating contents. Symptomatic reflux episodes (asthma, chronic cough, hoarseness) have a greater proximal extent compared to non-symptomatic reflux episodes. Proximal esophageal reflux is an important factor in persistent symptoms unsuccessful treated with proton pump inhibitors, especially when the reflux is non-acidic. Correctly performed impedance testing has an advantage for both the patient and the clinician in that the character and cause of the symptoms can be verified. During the test, the patient marks when hoarseness, cough or other symptoms occur, and it is later analyzed whether it correlates with reflux. It is possible that the patient's complaints are not due to reflux episodes, which necessitates further diagnosis and so the unsuccessful therapy with e.g. proton pump inhibitors can be discontinued.

LPRD TREATMENT

Correct therapy, which is successful and reduces the risk of recurrence in extraesophageal GERD, can be challenging for both

Tab. II. Addition of itopride to proton pump inhibitors in LPRD improves the efficacy of treatment and reduced the recurrence rate [23].

SYMPTOMS		IPP 40 MG ITOPRIDE 3 X 50 MG N = 42	IPP 40 MG + PLACEBO N = 45
Laryngological symptoms	Before treatment	**6.3** ± 1	**6.1** ± 1
	After treatment	**2.8** ± 0.5	**3.7** ± 1
Esophageal symptoms: heartburns, belching, dysphagia	Before treatment	**3.1** ± 0.4	**3.9** ± 0.5
	After treatment	**1.6** ± 0.4	**2.4** ± 0.7
Laryngeal pathology: edema, ulceration erythema, granulomas	Complete resolution	**20%**	**9%**
	Improvement	**40%**	**20%**
	Lack of impreovement	**8%**	**17%**
	Recurrence	**2%**	**11%**
Comprehensive laryngological examination	Before treatment	**4.4** ± 0.5	**4.6** ± 0.6
	After treatment	**1.2** ± 0.4	**2.8** ± 0.4

otolaryngologists and gastroenterologists. After confirming that the otolaryngological symptoms are related to reflux, the patient should be educated about the need of dietary modification and his or her health-promoting behavior should be verified [12–16]. The irrational restriction diet, promoted by some dieticians, should not be falsely recommended. This leads to microelement deficiencies. In most patient, small dietary changes can cause improvement (Fig. 1.).

Also, pharmacotherapy with the following drugs should be initiated.

Proton pump inhibitors (PPI)

PPIs constitute a golden standard in therapy of various forms of GERD [17]. In patients with extraesophageal GERD, it is recommended to initiate higher than usual doses of PPIs. In extraesophageal syndromes, PPIs do not affect the pathophysiological mechanism of reflux or the number of episodes; however, by blocking proton pumps they inhibit gastric production of acid. Considering the causes of reflux disease, it seems that inhibition of acid production is not always sufficient to alleviate symptoms.

Prokinetic agents – itopride (other prokinetics are not recommended for GERD)

Prokinetic agents promote upper gastrointestinal peristalsis and hence act on the most common causes of reflux.

Despite our positive experiences in everyday medical practice, prokinetic agents have not been yet included in practice guidelines for GERD. It can be due to the fact that itopride is relatively unknown in many European countries, where many experts come from. However, there are many studies confirming their efficacy with lower recurrence rate, especially regarding otolaryngological forms of GERD.

In pathogenesis of extraesophageal forms of GERD, proximal and non-acidic reflux can often be observed which leads to ineffective antacid treatment; therefore it seems reasonable to add prokinetic agents early in therapy together with PPIs. The combined therapy with PPIs and itopride alleviates reflux-related symptoms in extraesophageal or ‚otolaryngological' syndromes in shorter time compared to PPIs alone. The beneficial effect of itopride, which is currently the only safe prokinetic agent on the Polish pharmaceutical market, is based on increased lower esophageal sphincter. It also accelerates gastric emptying by increasing motility of gastric body, which leads to fewer reflux episodes. Therefore, the number of transient lower esophageal relaxations is reduced [18]. After oral administration, itopride is quickly absorbed and maximal serum concentration is observed after about 35 minutes. Its half-life time T1/2 is about 6 hours, and it is excreted mainly through kidneys as inactive metabolites. Itopride can also be applied in non-acidic reflux, because it acts regardless of the pH of the contents. Due to low risk of side effects, it can be used in long-term therapy [19]. Food does not affect its bioavailability, so it can be administered without any time regime regarding meals, i.e. it does not have to be taken on an empty stomach. The efficacy of itopride addition in treatment of otolaryngological forms of reflux disease has been confirmed by a randomized study comparing a 12-week course of proton pump inhibitor (lansoprazole 30 mg) combined with prokinetic agent (itopride 3 x 50 mg) against PPI monotherapy. The authors observed significant improvement with symptom reduction (confirmed by RSI score) [20]. In another randomized clinical trial, the authors compared the efficacy of an 8-week course of proton pump inhibitor (pantoprazole 40 mg) combined with itopride (3 x 50 mg) against pantoprazole with placebo. After 16 weeks of follow-up and photographic documentation, it was concluded that addition of itopride to PPI therapy alleviates symptoms such as cough, grunting, globus sensation (RSI), as well as some morphological changes of the larynx (Belafsky's RFS score). It was also established that LPRD recurrence was reduced after addition of itopride to PPI [21].

Healing and protecting agents

The so-called added therapy should be considered in extraesophageal GERD. On our local pharmaceutical market, there are medications acting locally on the mucosa and protecting it against acid, which contain hyaluronic acid and chondroitin sulfate; they promote healing and moisturize the pharyngeal and laryngeal mucosa.

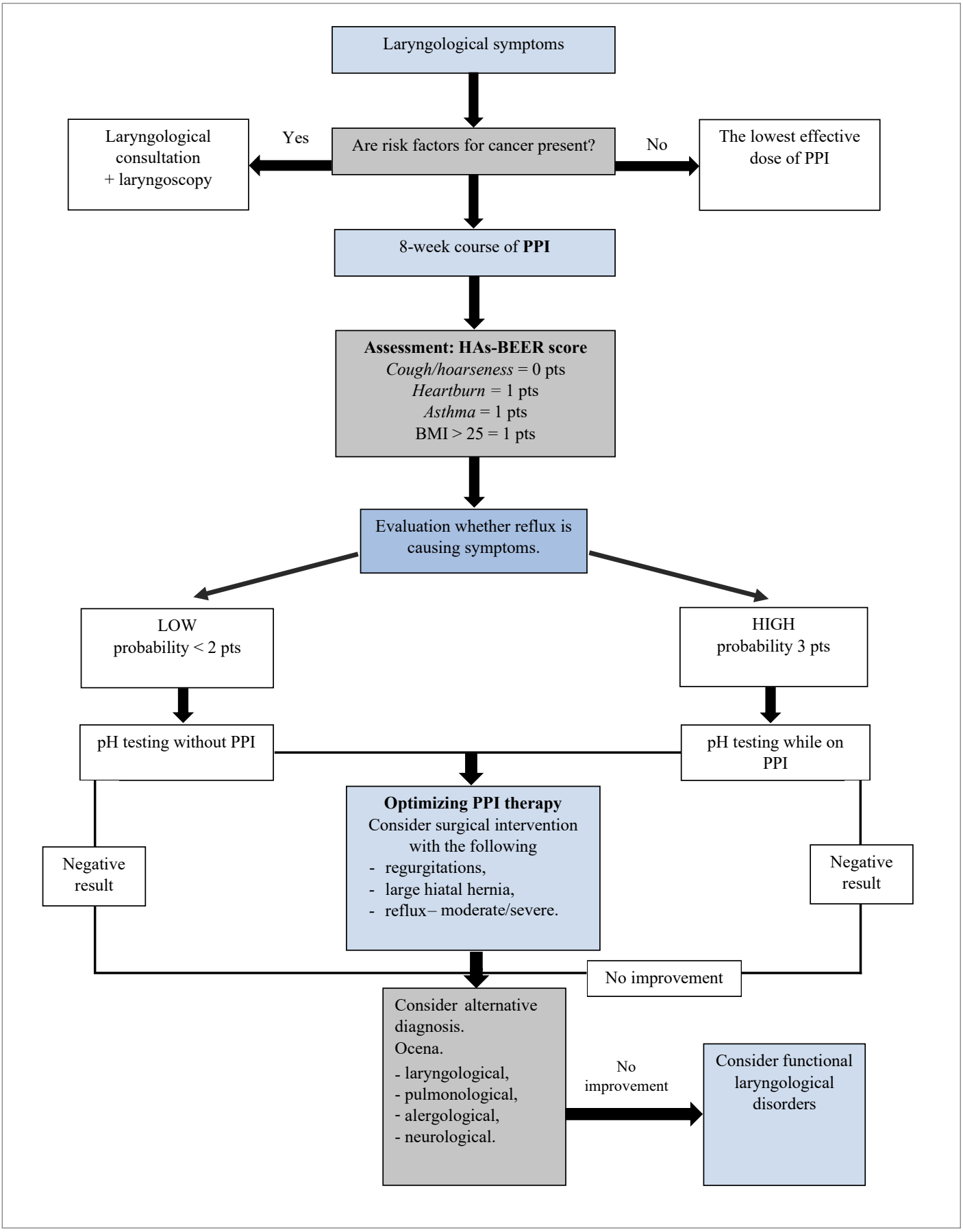

Fig. 2. Diagnostic and therapeutic algorithm in patients with laryngological symptoms, modified by Prof. Gąsiorowska [24, 25].

Alginates and antacids

They neutralize acidic outer layer of food and significantly recede the zone of pH change from the gastroesophageal junction, and their actions is consistent with the pathology of the disease. Surgical treatment is not recommended for extraesophageal symptoms of GERD in patient not responding to gastric acid inhibition with PPIs [11]. Not all patients with laryngological symptoms relating to reflux disease will achieve therapeutic success with antireflux surgery. Surgical intervention is often beneficial in patients who have numerous reflux episodes confirmed by impedance testing [22, 23].

SUMMARY

Adding itopride to proton pump inhibitor in treatment of extraesophageal forms of reflux disease shortens duration of treatment, improves its efficacy and reduced the risk of relapse. Itopride can be applied regardless of the chemical properties (high pH) of the reflux contents. There is often proximal and non-acidic reflux observed in laryngopharyngeal forms of GERD, and hence it seems reasonable to add prokinetic agents in early therapy together with PPIs. This approach may alleviate otolaryngological symptoms earlier in patients.

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Corresponding author: Maria Janiak MD PhD (ORCID: 0000-0003-4949-3128); Department and Clinic of Gastroenterology and Hepatology, Medical University of Gdansk; Smoluchowskiego street 17, 80-214 Gdansk, Poland; Phone: +48 58 349 36 40; E-mail: maria.janiak@gumed.edu.pl

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