

## Laryngopharyngeal Reflux and Asthma

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### Abstract

The gastroesophageal reflux presence in asthma has been the subject of many studies indicating their frequent coexisting. The essence of this correlation is not entirely clear and several hypotheses can be found in literature. Recently defined laryngopharyngeal reflux and studies on its impact on the course of asthma seem to bring us closer to understanding this issue. In the last years we gained access to the new diagnostic methods allowing direct registration of laryngopharyngeal reflux. This paper summarizes laryngopharyngeal reflux diagnostic possibilities including the most advanced technologies. It also evaluates published clinical studies, which investigated laryngopharyngeal reflux in asthma patients, both in adults and children.

**Keywords:** Laryngopharyngeal reflux; Asthma; pH-monitoring; Impedance; Dx-pH

### Introduction

Laryngopharyngeal reflux (LPR) is usually defined as the passage of the gastric contents through the esophagus into the pharynx and/or larynx that causes troublesome symptoms and/or complications. Although the LPR has been suspected to be one of exacerbating factors for asthma over the past few decades, the real association between these two common diseases has not been established yet. There are many studies that investigated gastroesophageal reflux (GER), which is defined as the retrograde flow of gastric contents into the esophagus, in asthma patients [1-3], but only a few of them were dedicated to the assessment LPR. This article focuses on the findings about clinical studies assessing LPR in patients with asthma in both adults and children.

### Etiopathogenesis

There are many potential mechanisms of mutual influence between asthma and LPR. Predisposition factors of reflux occurring in patients with asthma generally include: weakened the lower esophageal sphincter (LES)-barrier by an increased negative pressure in the thorax, autonomic dysregulation with heightened vagal tone, transient LES relaxations (TLESRs) due to airway obstruction and reduction of LES pressure by asthma medications e.g.  $\beta_2$ -adrenergic agonists [4-6].

The factors that contribute to the occurrence of asthma or its exacerbations in patients with reflux include: vagal esophago-bronchial reflex, local neuronal reflexes, microaspirations that cause increased bronchial reactivity and bronchoconstriction, direct induction of respiratory epithelium inflammation by the refluxate [7-10]. Although all these factors suggest that LPR may play a substantial role in the clinical manifestation of asthma, the exact relationship between the two diseases remains indefinite.

### Diagnostic Methods

Laryngopharyngeal reflux initial diagnosis is essentially based on the assessment of clinical picture, which appears to be different from gastroesophageal reflux disease (GERD). Usually it does not include complaints from the upper gastrointestinal tract, e.g. heartburn, abdominal pain, nausea, and postprandial bouncing. Predominant symptoms of LPR are mostly limited to ear, nose and throat (ENT), and pulmonological symptoms such as hoarseness, chronic cough, postnasal drip, throat-clearing, sensations of something sticking in the

throat or even choking episodes and breathing difficulties. The severity of these complaints can be evaluated using various scales [11]. However, the most widely used and best validated is the Reflux Symptoms Index (RSI) [12]. RSI questionnaire contains 9 symptoms, which are rated by the patient according to the severity of those ailments. Total score above the defined threshold indicates a high probability of the LPR diagnose, but does not guarantee it [13].

The initial assessment of LPR in adults is often based (similarly as in GERD) on the empirical treatment with high doses of proton pump inhibitors (PPI) [14]. However, there is no clear consensus on effectiveness, dosage and length of this treatment [15-17]. Moreover, empirical management seems to be associated with poor compliance in comparison with the treatment preceded by a diagnosis based on pH-monitoring [18].

In order to objectify and refine the diagnosis, endoscopic and functional examination can be used. In ENT specialist practice it is commonly laryngoscopy, which may reveal posterior laryngitis, swelling of the vocal folds (Reinke's edema), vocal cord nodules, mucosal metaplasia ("white-line") or laryngeal pseudo-sulcus and ulceration [19]. These signs are summarized in reflux finding score (RFS) scale [20], but none of them is characteristic only of LPR (RFS sensitivity at most is up to 88% and specificity up to 38%) [21,22]. Similarly, esophageal mucosa damage revealed in esophagogastroduodenoscopy may also occur in other conditions (e.g. GERD, eosinophilic esophagitis). Moreover, esophagitis is present in less than 20% of patients with LPR [23].

Another group of LPR diagnostic methods consists of widely used functional tests, which measure pH in the upper part of gastrointestinal tract. This allows direct observation of retrograde bolus migration. The main disadvantage of most of these tests is the lack of measurement in laryngopharyngeal region, which seems to be crucial for LPR diagnosis.

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Classical pH-metry ("gold standard" in GERD diagnostic work-up) records the pH drops only in the distal esophagus. In its dual-probe version, the measurement range is extended to the upper esophageal sphincter (UES), but it does not exceed it. Furthermore, proper placement of proximal sensor is difficult and artifacts of drying of the electrode are present, therefore dual-pH is not recommended in the guidelines [24,25]. Multichannel intraluminal impedance (MII) also does not allow pharyngeal pH recording; however, it is very valuable in assessing character and propagation of the refluxate [26].

Only a few new techniques enable determining pH exactly in the oropharynx. The pharyngeal pH-metry (Dx-pH) has a teardrop shape sensor, which detects aerosolized as well as liquid contents, resists drying and mucus covering [27]. Dx-pH is positioned without a need for X-ray, manometry or endoscopy guidance, but it only measures the pH in the oropharynx without correlation with GER. This disadvantage does not apply to the hypopharyngeal multichannel intraluminal impedance (HMII), which additionally distinguishes acid and non-acid refluxes [28.] However, HMII has been introduced very recently and requires further testing. Remaining doubts concern the origin of the pH drops in oropharynx, which do not always correlate with observed episodes of GER [29].

There are possibilities of determining the presence of pepsin and other digestive enzymes in the respiratory tract, saliva or in exhaled breath, but so far they are neither validated nor widely used [30-32].

Despite several attempts, the multitude of diagnostic procedures results in an absence of clearly defined standards of LPR diagnostic. Nonetheless, monitoring pH above the UES in hypo/oropharynx seems to be the most acknowledged and reliable evaluation method.

## Clinical Studies

The number of studies assessing the association between LPR and asthma is limited and they are very heterogeneous. Lack of standardized definitions for LPR and asthma symptoms, small sample size, absence of control group and variation in age groups limit the value of these studies. However, the main findings of these studies are summarized below.

Eryuksel et al. in their study from 2006 enrolled 28 adults with asthma. The diagnosis of LPR was based on symptoms assessment and videolaryngoscopy [33]. LPR was present in 75% (21/28) of cases. In these patients PPI treatment (pantoprazole for 3 months) was administered with statistically significant improvement both in the symptoms of asthma and LPR. Despite the small study group and the lack of a control, this paper shows a high prevalence of LPR in asthma and the potential effectiveness of PPI treatment.

In 2007 Wiener et al. published their study on Dx-pH monitoring in detection of LPR in patients with extraesophageal symptoms (2 of them had asthma) [34]. The researchers conducted a simultaneous dual-channel pH-metry and Dx-pH. LPR was present in one patient with asthma (1/2, 50%).

In the Makosiej et al. study of children with chronic inflammation of respiratory system, 3 patients had asthma [35]. Based on Dx-pH evaluation in 2 cases (66%) LPR was confirmed. In both of the above pilot studies very small groups of patients were examined, which makes it problematic to draw any conclusions.

Onyekwere's et al. paper from 2010 compared the results of reflux symptoms basing on questionnaires filled in by 98 adults with asthma and 71 controls [36]. Additionally, Dx-pH monitoring in 12 cases (5

with asthma) was performed. There were no statistically significant differences between the two groups, with the prevalence of reflux of 30–35% (based on symptoms). Moreover, reflux was confirmed by pH-metry only in 80% (4/5) of asthmatics and in 100% of controls. As in the previous study, the patient group was very small.

In 2011, Banaszekiewicz et al. conducted a clinical study involving 21 children with difficult-to-treat asthma [37]. LPR was diagnosed in more than 60% of patients. Positive correlation between the diagnosis of LPR and degree of asthma control ( $p=0.012$ ) as well as intensity of treatment was demonstrated. The main limitation of the study was the relatively small group of patients, although it was statistically sufficient.

In 2013, Kilic et al. published their study on correlation of asthma and LPR [38]. 50 children (from 150 diagnosed with asthma) were randomly enrolled and divided in two groups according to the asthma control status—controlled and uncontrolled asthma. Double probe pH monitoring and laryngoscopy were performed. In 70% of patients LPR was diagnosed, but there was no statistically significant difference between the two groups ( $p=0.8$ ). Additionally, laryngeal findings did not enable the researchers to differentiate between children with and without LPR. As in the previous papers, the study group was relatively small.

Komatsu et al. performed HMII on patients with adult-onset asthma [39]. 70% of 31 subjects had abnormal proximal pH exposure in upright body position, which was considered, despite the cases of normal values of composite score, an evidence of extra-esophageal reflux. 20 patients underwent antireflux surgery with the outcome of asthma symptoms reduction in 90% of cases. This study confirmed the high prevalence of reflux in patients with asthma and also seems to prove causality of this relation.

There are numerous studies, performed with dual pH-probes or MII, on coexistence of asthma and GERD, but their review was not a purpose of this paper.

## Conclusions

This article reveals a paucity of clinical data regarding the association between LPR and asthma. There are only a few studies with small or very small samples, without control group and providing varying disease definitions. Moreover, different techniques for LPR detection were used in these studies. All together, they do not allow firm conclusions to be drawn on the role of LPR in asthma. More well-planned studies are strongly needed to establish it.

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