

## Gastroesophageal reflux disease related asthma: From preliminary studies to clinical practice

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### Abstract

The diagnosis of asthma requires the presence of episodic respiratory difficulties characterized by variable and reversible airway obstruction. It has a high prevalence worldwide and is traditionally considered to be an allergic disease. Most cases are responsive to treatment with bronchodilators and anti-inflammatories, as recommended

by national and international guidelines; however, approximately 10% of asthmatic patients are refractory even to optimal therapy. Gastroesophageal reflux disease (GERD) is a common disorder in asthmatic patients and the two disorders may be linked pathophysiologically. Here we review data from preliminary studies that suggest asthma could be induced or exacerbated by gastroesophageal reflux. The optimal strategies for the diagnosis of GERD-related asthma and its therapy are still debated. However, there is evidence to suggest that antireflux treatment is effective and practical for asthmatic patients with well-defined reflux disease.

**Key words:** Asthma; Gastroesophageal reflux disease; Proton pump inhibitors; Laparoscopic fundoplication

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**Core tip:** Allergic responses have been extensively studied but may be overemphasized for asthma; some asthma is frequently found to be associated with gastroesophageal reflux disease (GERD) rather than "allergy". That a subgroup of asthma could be induced or exacerbated by gastroesophageal reflux has become consensus. GERD should be assessed in asthmatic patients who also have typical symptoms of GERD, as well as in patients with nonatopic or severe/refractory asthma. The optimal strategies for the diagnosis of GERD-related asthma and its therapy are still being debated. However, there is evidence to suggest that antireflux treatment is effective and practical for asthmatic patients with well-defined reflux disease.

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## ASTHMA AS A RESPIRATORY DISEASE

A patient was characterized as having paroxysmal dyspnea with wheezing and repeated cough, particularly at night and in the early morning. Further testing demonstrated reversible airflow limitation: the diurnal variation in the peak expiratory flow rate was  $\geq 20\%$  and the forced expiratory volume in one second was increased by  $\geq 12\%$  and  $\geq 200$  mL in absolute volume by  $\beta^2$  agonist inhalation and a positive methacholine challenge test, respectively. In this case, the diagnosis of asthma can be readily established<sup>[1]</sup>. Asthma is a serious problem that affects 235 million people, according to WHO estimates. It remains under-diagnosed and under-treated, creating a substantial burden of morbidity to individuals and families and potentially restricting activities for a lifetime<sup>[2]</sup>. It is also one of the most costly chronic conditions, both financially and in terms of human lives, being responsible for an estimated 15 million daily-adjusted life years lost annually and having a role in one of every 250 deaths worldwide<sup>[3]</sup>.

Classically, asthma is considered as a Th2-associated eosinophil-predominant atopic disease. However, the true pathophysiological picture is less straightforward, with asthma representing a complex group of conditions. Efforts have been made to define and classify phenotypes/endotypes based on the age of onset, duration, severity and presence of allergy amongst other factors<sup>[4-9]</sup>. Recently, a Th17-mediated neutrophil-predominant phenotype with more severe disease that may be less responsive to steroids was described, in which increased glucocorticosteroid receptor (GR) signaling and oxidative stress were suggested as mechanisms of steroid resistance<sup>[10]</sup>.

The cellular and molecular biology of asthma are targeted by respiratory physicians in asthma therapy. Removal of predisposing factors and stepwise pharmacotherapy based on the assessment of disease severity form the mainstay of asthma management, with the goals of maintaining symptom control, attaining pulmonary function that is as close to normal as possible, and reducing mortality. Anti-inflammatory treatment with inhaled corticosteroids comprises a key component of treatment in asthma<sup>[11]</sup>. Unfortunately, about 10% of asthmatics appear to have refractory disease despite receiving optimal therapy, leading to increased morbidity and increased costs associated with treatment<sup>[12-14]</sup>. In poorly controlled asthma, add-on therapies used as part of combination treatment include bronchodilators, mainly long-acting  $\beta$ -agonists but also theophylline or new biological therapies, such as humanized antibodies against IgE, interleukin 5 and interleukin 4R/13; such therapeutic strategies offer hope to improve the quality of life and long-term prognosis of severe asthmatics with specific molecular phenotypes. A new promising procedure, bronchial thermoplasty, is available for severe asthma and studies are ongoing to find the optimal responders to this technique<sup>[9,15]</sup>.

Real progress has been made in identifying patients with asthma and in understanding its biological basis and treatment. However, the fundamental causes of asthma are still not understood and the treatment therefore focuses on providing symptomatic relief and improvement of lung function and airway responsiveness. They do not prevent exacerbations or disease progression and asthma is still considered incurable. Allergic responses that often substantially contribute to both chronic persistent asthma and acute exacerbations have been extensively studied but may be overemphasized<sup>[2,16]</sup>. By contrast, when studied by physicians other than respiratory specialists, some asthma is frequently found to be associated with gastroesophageal reflux disease (GERD), rather than with "allergy". Theoretically, GERD and asthmatic symptoms may be connected through mechanisms including micro-aspiration and both local and central reflexes<sup>[17]</sup>. In addition, increased gastroesophageal reflux and impaired function of the upper esophageal sphincter may contribute to more transpharyngeal spray and microaspiration, in turn leading to airway irritation, inflammation and hyper-responsiveness, which may cause or increase the severity of asthma<sup>[18]</sup>.

## EXTRAESOPHAGEAL GERD SYMPTOMS

A global evidence-based consensus by gastroenterologists defined GERD as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications<sup>[19]</sup>. Furthermore, the established associations between asthma and GERD were acknowledged, with asthma being recognized as one of the extraesophageal GERD syndromes. The possibility of reflux of gastric contents into the esophagus or beyond into the oral cavity (including the larynx) or lung is significant in this regard and the spectrum of clinical presentations attributed to GERD has expanded from typical esophageal symptoms of heartburn and regurgitation to an assortment of extraesophageal manifestations, including respiratory and laryngeal symptoms. A series of recommendations for extraesophageal symptoms has been made by the consensus. First, GERD can be considered as a potential co-factor in patients with asthma, chronic cough or laryngitis but a diagnosis of reflux laryngitis should not be made based solely upon laryngoscopy findings. Upper endoscopy is not recommended as a means to establish a diagnosis of GERD-related asthma, chronic cough or laryngitis. A trial of proton pump inhibitors (PPI) is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD; reflux monitoring should be considered before such a trial in patients with extraesophageal symptoms who lack typical symptoms of GERD and non-responders to a PPI trial should be considered for further diagnostic testing. Surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with a PPI<sup>[20]</sup>.

## LARYNGOPHARYNGEAL REFLUX

Laryngopharyngeal reflux (LPR) is a common problem encountered by otolaryngologists. LPR is defined as the association of laryngeal symptoms with laryngeal inflammation at laryngoscopy<sup>[21]</sup>. The esophageal mucosa with its intrinsic antireflux defenses can temporarily bear insults of reflux without anatomical modifications of the epithelium, whereas the respiratory mucosa is not resistant to acid injury even in the context of a limited period of exposure. As such, all types of reflux (acid, non-acid, liquid, mixed and air) detected by impedance changes probably should be considered in the diagnosis of LPR. The retrograde flow of the stomach contents up to the throat is associated with many otolaryngological disorders, such as reflux laryngitis, cervical dysphagia, globus pharyngeus, chronic cough, laryngeal or tracheal stenosis, laryngeal carcinoma and asthma. A trial of double dose PPI therapy for 3 mo was found to be valuable for atypical GERD symptoms related to LPR. However, the diagnosis of LPR can rely neither on esophageal investigations (endoscopy, pH/impedance monitoring) nor on the response to high dose PPI because of a prominent placebo effect. There is a need for the development of new tools to better identify the subgroup of patients with laryngeal symptoms related to supra-esophageal reflux<sup>[22-27]</sup>.

## PEDIATRIC STUDIES

Pediatricians found that GERD is highly prevalent in children with asthma, with estimates as high as 80%, but nearly half of the children are asymptomatic. There is no conclusive evidence that asymptomatic GERD informs asthma control and treatment of GERD in the few controlled trials available for review does not substantially improve asthma outcomes. In a recent large controlled clinical trial, treatment with a PPI was not only ineffective, but adverse effects were common, including an increased prevalence of symptomatic respiratory infections. Current evidence therefore does not support the routine use of anti-GERD medications in the treatment of poorly controlled asthma of childhood. However, large controlled trials of children symptomatic with both GERD and asthma have not been conducted and, in this case, the benefits of treatment, although unproven, might outweigh the risks<sup>[28]</sup>. There is a possible association between GERD and asthma in pediatric patients seen with asthma in referral settings. However, because of methodological limitations of existing studies and the paucity of population-based and longitudinal studies, several aspects of this association are unclear<sup>[29]</sup>.

## ANTIREFLUX SURGERY FOR ASTHMA

Many uncontrolled studies have been undertaken

to investigate the effect of antireflux surgery on asthma outcome. The results of these studies suggest that surgery could improve asthma symptoms and medication use in 80%-90% of asthmatics and could also improve pulmonary function in approximately 25%. In these reports, a small proportion of the patients were "cured" of their asthmatic symptoms without any medication<sup>[30]</sup>. However, there are only a small number of controlled studies. Sontag *et al.*<sup>[31]</sup> compared fundoplication to ranitidine and to placebo in asthma patients with GERD. Asthma symptoms and medication requirements improved postoperatively but peak expiratory flow only improved by 10% in one third of the patients. This study was never published as a complete report. A second controlled study with cimetidine noted that drug therapy and surgery for GERD were both associated with an improvement in asthma symptoms and medication requirement at 6 mo but not with any statistical significant improvement in pulmonary function compared with placebo<sup>[32]</sup>. A third study, again assessing ranitidine, showed that 74.9% of patients in the surgery group improved compared with 9.1% of the medical group and 4.2% of the control group<sup>[33]</sup>. Recently, Sontag *et al.*<sup>[33]</sup> compared floppy Nissen to Toupet fundoplication. Symptom scores of cough, asthma, hoarseness and distortion of taste had similar substantial improvements at 3 and 12 mo follow-up after surgery. In related studies, GERD and recurrent microaspiration have been noted to be common and often severe among patients with advanced lung disease; following lung transplantation, both GERD and aspiration appear to be risk factors for the development of bronchiolitis obliterans syndrome and selected patients may benefit from antireflux surgery<sup>[34]</sup>.

For children, a study by Khoshoo *et al.*<sup>[35]</sup> found that PPI/prokinetics or fundoplication in older children with GERD and persistent asthma resulted in a significant reduction in the requirement for asthma medications. Another controlled study by Khoshoo *et al.*<sup>[36]</sup> found fundoplication and esomeprazole/metoclopramide to be associated with significantly fewer exacerbations of asthma symptoms in children with moderate persistent asthma and concomitant GERD when contrasted with ranitidine treatment. Recently, a study by Rothenberg *et al.*<sup>[37]</sup> examined the laparoscopic fundoplication (LF) outcome of 235 children with severe steroid-dependent asthma and medically refractory GERD. A significant subjective improvement in respiratory symptoms was noted by 215 patients (91%) by the time of the first postoperative visit at 2 wk. Eighty percent were successfully weaned off their oral steroids within the first 2 postoperative months and 95% reported a decrease in their inhaler use. A symptomatic improvement at follow-up (2 to 72 mo postoperatively, with an average of 48 mo) was noted by 209 patients (89%) and 99% of those with nocturnal asthma observed a disappearance or significant decrease in their nighttime symptoms.

No intraoperative complications or postoperative respiratory tract infections occurred.

## GERD DEPARTMENT PRACTICE FOR ASTHMA

GERD-related asthma has been studied since 2006 in our GERD department, where patients with severe or refractory asthma are screened for GERD using dual 24 h esophageal pH monitoring, endoscopy and high-resolution manometry. We have applied radiofrequency energy to the gastroesophageal junction (Stretta procedure) in more than 1600 cases and have used LF in over 1800 GERD patients in 8 years<sup>[38]</sup>. Our study of LF on GERD-related respiratory symptoms showed an excellent outcome with respect to respiratory symptoms after surgery in 35.9% of cases, a good outcome in 43.8%, fair in 7.8% and poor in 12.5%; accordingly, the mean respiratory symptom score decreased from  $6.3 \pm 2.65$  to  $2.33 \pm 2.37$  at a mean follow-up of 12 mo<sup>[39]</sup>. Our surgical outcome was similar to that reported by other groups<sup>[28]</sup>. Another study of the Stretta procedure for 505 patients with wheezing and chronic cough resulted in a wheezing score reduction from 7.83 to 3.07, a cough score reduction from 6.77 to 2.85, and heartburn score reduction from 5.31 to 1.79 ( $P < 0.01$ ) at a mean follow-up of 12 mo<sup>[40]</sup>. Recently, the five year outcome of the Stretta procedure was reported. The heartburn, regurgitation, chest pain, cough and asthma scores were all significantly decreased compared with the corresponding values before the procedure ( $P < 0.001$ ). After the Stretta procedure, 59 (42.8%) patients achieved complete PPI therapy independence and 104 (75.4%) patients were completely or partially satisfied with their GERD symptom control. No prolonged severe complications were observed<sup>[41]</sup>. Comparing the long term outcomes of the Stretta procedure and LF, we found that both LF and the Stretta procedure are capable of controlling symptoms effectively and safely in selected patients; LNF gave more improvement in regurgitation, heartburn, chest pain, belching, hiccupping, cough, asthma and PPI elimination, whereas the Stretta procedure is less invasive<sup>[42,43]</sup>. We also found that the Stretta procedure and LF are both effective treatments for GERD-related childhood-to-adult persistent asthmatic patients who had an inadequate response to medical treatment for asthma<sup>[44]</sup>. Two children who had difficult-to-treat asthma were cured by antireflux interventions<sup>[45]</sup>; active antireflux treatments can also be beneficial for patients with bronchiectasis and cough syncope, reducing their disabling respiratory symptoms<sup>[43,46]</sup>.

## DIAGNOSIS AND MANAGEMENT OF GERD-RELATED ASTHMA

The ultimate causes of asthma remain poorly understood, with little consensus about the relative importance of

different putative causal factors. If asthma, chronic obstructive pulmonary disease (COPD) and bronchitis, as well as emphysema and bronchiectasis, are considered merely as components of airway disease<sup>[47]</sup>, it is reasonable to diagnose some cases of asthma as manifestations of one of the most important extraesophageal symptoms of GERD (or GERD as one of the most important factors of asthma acceleration). Theoretically, GERD-related asthma can be defined as asthmatic symptoms being induced or exacerbated by gastroesophageal reflux. Thus, the diagnosis and treatment of this entity may not be adequately managed through reliance on current asthma guidelines alone because GERD is at best inadequately addressed in these guidelines<sup>[11,48]</sup>. Since the evaluation of patients for possible treatment of the underlying causes such as GERD can improve symptoms or even cure the disease, GERD should be assessed in asthmatic patients who also have typical symptoms of GERD, as well as in patients with nonatopic or severe/refractory asthma<sup>[37,44]</sup>.

Diagnosing GERD as the cause of GERD-related asthma has proven to be very challenging<sup>[20,49]</sup>. The presence of typical GERD symptoms and current available tests for GERD, such as upper endoscopy and ambulatory reflux monitoring, are widely used for extraesophageal reflux evaluation and esophageal manometry is also recommended for fundoplication candidates, although these tests have uncertain sensitivity and specificity for the diagnosis of GERD-related asthma. PPI treatment may be a reasonable therapeutic and diagnostic tool for patients with asthma who also have typical symptoms of GERD or objective evidence of GERD by endoscopy or reflux monitoring and higher dose PPI (twice daily) has been recommended. However, few well-defined markers are available to predict which patients will respond to therapy and empirical treatment for patients without typical symptoms or objective evidence of GERD cannot be routinely recommended. A good response of asthmatic symptoms to PPI treatment may permit a more confident diagnosis of GERD-related asthma and failure to respond to a 2-3 mo course of PPI should prompt a careful re-assessment of the patient, with consideration of other causative factors for the asthmatic symptoms<sup>[20]</sup>. Various biomarkers in different types of biosamples have been studied in the context of extraesophageal reflux; however, they are still not available for routine clinical practice. Inflammatory biomarkers differ in asthmatics based on reflux status. For example, tachykinins are elevated in patients with GERD-related cough and bile acids are elevated in lung transplant patients with GERD. However, studies like these are often limited by their small size, methods of analysis and case selection. Bronchoalveolar lavage is too invasive to be of use in most patients; exhaled breath condensate samples need further evaluation and standardization and the particles in exhaled air measurements need to be studied further. It is clear

that a reliable test to identify GERD-induced respiratory disorders needs to be developed<sup>[50]</sup>.

PPI treatment is commonly recommended for suspected GERD-related asthma and some patients may respond well to PPI therapy. However, studies to date have shown only limited benefits for the treatment of symptomatic GERD on asthma outcomes and many well-designed studies have failed to demonstrate clear benefit on asthma control<sup>[28,51,52]</sup>. Potential reasons for the failure of PPI treatment to elicit a response include a lack of compliance with the medication regimen, impaired gastric accommodation, delayed gastric emptying, nocturnal gastric acid breakthrough and rapid drug metabolism. In addition, reflux of non-acidic gastric contents (*e.g.*, pepsin, bile acids and pancreatic enzymes), mechanical distention of the esophagus or sensory nerve hyperalgesia may act as a predominant mechanism in eliciting symptoms in the patients with asthma that is resistant to PPI treatment<sup>[53]</sup>.

In developed countries, laparoscopic antireflux surgery is commonly used for resolving persistent symptoms of heartburn and regurgitation in GERD, especially when it is refractory to PPI treatment<sup>[54,55]</sup>. For GERD-related asthma, an improvement of asthma control was achieved in over 80% of asthmatic patients after fundoplication<sup>[30,32,37,44,56]</sup> and radiofrequency energy application to the gastroesophageal junction is another potentially effective therapy for GERD-related asthma<sup>[40-42,44,57]</sup>. LF has been recommended by gastrointestinal and endoscopic surgeons for patients with extraesophageal manifestations (asthma, hoarseness, cough, chest pain, aspiration), especially with evidence of volume regurgitation or any sizable hiatal hernia. LF is safe with fewer complications, especially when performed by skilled surgeons with extensive experience in this procedure<sup>[58,59]</sup>. Studies of the outcomes of surgical treatment may be harder to interpret in the tradition of evidence-based medicine as they suffer from a lack of controls and blinding; surgical protocols may also use different postoperative evaluation criteria and are typically based on a highly selected group of patients. However, surgical restoration of the anatomical antireflux barrier at the gastroesophageal junction is a more effective method of avoiding any type of gastroesophageal reflux theoretically and is superior to PPI therapy. A failure of PPI treatment may only mean that acid inhibition for reflux was insufficient to provide a therapeutic effect and that surgical intervention could be a better choice after careful evaluation<sup>[18]</sup>.

## CONCLUSION

The pathophysiology of asthma and GERD, as well as the relationships between them, is much more complex than was initially thought and is far from being adequately elucidated. Data from preliminary studies are now available to support the concept that asthma could induce or be exacerbated by gastroesophageal reflux. However, the causative mechanisms are very difficult to evaluate and upper endoscopy, ambu-

latory reflux monitoring, laryngoscopy, esophageal manometry and PPI trials all have limited utility in the comprehensive evaluation of extraesophageal reflux. The diagnosis of GERD-related asthma is therefore still experimental. High dose PPI treatment is recommended for GERD-related asthma and antireflux surgery is effective and practical for asthmatics with well-defined reflux disease, preferably done by a skilled, experienced surgeon. Improved tests for diagnosing GERD-related asthma and objective assessment of the effects of the surgery on asthma control are required and are the focus of further study.

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