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EXPERT REVIEWS

Extra-esophageal gastroesophageal reflux disease and asthma: understanding this interplay

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Gastroesophageal reflux disease (GERD) is a condition that develops when there is reflux of stomach contents, which typically manifests as heartburn and regurgitation. These esophageal symptoms are well recognized; however, there are extra-esophageal manifestations of GERD, which include asthma, chronic cough, laryngitis and sinusitis. With the rising incidence of asthma, there is increasing interest in identifying how GERD impacts asthma development and therapy. Due to the poor sensitivity of endoscopy and pH monitoring, empiric therapy with proton pump inhibitors (PPIs) is now considered the initial diagnostic step in patients suspected of having GERD-related symptoms. If unresponsive, diagnostic testing with pH monitoring off therapy and/or impedance/pH monitoring on therapy, may be reasonable in order to assess for baseline presence of reflux with the former and exclude continued acid or weakly acid reflux with the latter tests. PPI-unresponsive asthmatics, without overt regurgitation, usually have either no reflux or causes other than GERD. In this group, PPI therapy should be discontinued. In those with GERD as a contributing factor acid suppressive therapy should be continued as well as optimally treating other etiologies requiring concomitant treatment. Surgical fundoplication is rarely needed but in those with a large hiatal hernia, moderate-to-severe reflux by pH monitoring surgery might be helpful in eliminating the need for high-dose acid suppressive therapy.

KEYWORDS: asthma • extra-esophageal reflux • fundoplication • pH monitoring • proton-pump inhibitor

Gastroesophageal reflux disease (GERD), as defined by the Montreal Classification, is the reflux of stomach contents that leads to symptoms of heartburn and regurgitation [1]. These defined esophageal symptoms affect 35–40% of the adult population in the western world and are in dichotomy with extra-esophageal symptoms of GERD (**Box 1**) [2–4]. These extra-esophageal symptoms include asthma, laryngitis, cough and dental erosions [3,5]. Diagnosing extra-esophageal GERD can be difficult due to the lack of heartburn or regurgitation, which can be absent in 40–60% patients with asthmatics, 57–94% of patients with otolaryngology complaints and 43–75% of patients with chronic cough [1–3,5,6]. These symptoms have a significant economic burden, with an average cost of caring for patients with extra-esophageal symptoms of over US$50 billion, which is five-times that of patients with GERD (**Figure 1**) [7]. The most recent census data revealed that asthma affects 25.7 million people, including 7.0 million patients under age 18 [8]. Asthma's prevalence continues to rise from 3.1% in 1980, 5.5% in 1996, 7.3% in 2001 and 8.4% in 2010; therefore, imposing a significant health and economic burden [9].

As the evidence for the association of GERD and asthma increases, this area continues to have strong academic pursuits to better understand the relationship in order to provide effective treatment. In this review, we highlight the state-of-the-art knowledge on pathophysiology, role of diagnostic testing and current treatment options for those suspected with asthma and extra-esophageal manifestations GERD. We will highlight the controversy that resides in the current treatment options for this disease entity and portray treatment options for sub-group of patient with

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Box 1. Esophageal and extra-esophageal manifestations of gastroesophageal reflux disease.

Esophageal syndromes

- Symptomatic syndromes
  - Typical reflux syndrome
  - Reflux chest pain syndrome
- Syndromes with esophageal injury
  - Reflux esophagitis
  - Reflux stricture
  - Barrett's esophagus
  - Adenocarcinoma

Extra-esophageal syndromes

- Established association
  - Reflux asthma
  - Reflux laryngitis
  - Reflux cough
  - Reflux dental erosions
- Proposed association
  - Sinusitis
  - Pulmonary fibrosis
  - Pharyngitis
  - Recurrent otitis media

Adapted from the Montreal Classification of gastroesophageal reflux disease [1].

suspected extra-esophageal GERD who may benefit from acid suppressive therapy.

Which asthmatics are likely to have extra-esophageal GERD?

The prevalence of GERD in 25.7 million people with asthma is estimated to be 32–82% [10–13]. A causal relationship between GERD and asthma is difficult to establish since either condition can induce the other (Figure 2) [14–16]. One should suspect GERD-induced asthma in patients with asthma presenting initially in adulthood, poor control of asthma with medications, onset of heartburn or regurgitation before asthma events, worsening asthma events with eating large meals, drinking alcohol or bring in supine position [17].

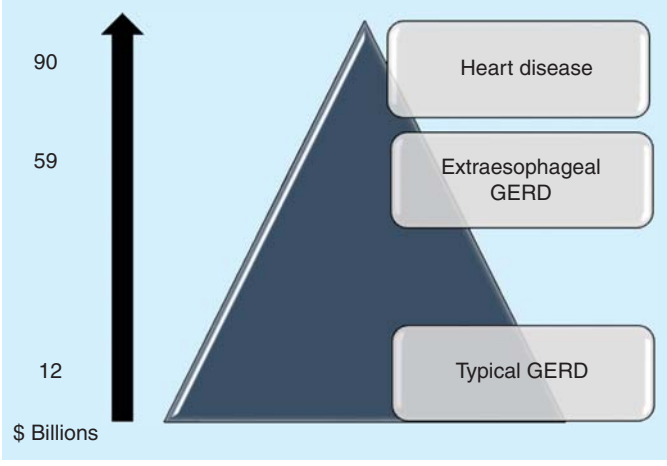

Figure 1. Economic burden of extra-esophageal GERD.
GERD: Gastroesophageal reflux disease.

A significant portion of patients with asthma also exhibit typical symptoms of gastroesophageal reflux (GER), such as heartburn and regurgitation. In those with chronic cough, lack of the classic symptoms does not rule out physiologic acid reflux [18]. Havemann *et al.* found that the average prevalence of GERD in asthma was 59.2%, a potential underestimation since many patients may not exhibit typical symptoms of reflux [19]. Another study by Kiljander *et al.* found that 35% of asthma patients in their study did not have typical reflux symptoms, but were instead found to have reflux by 24-h esophageal pH monitoring [20]. Thus, reflux is likely even if patients do not complain of typical symptoms such as heartburn and regurgitation.

Pathophysiology

The interplay between asthma and extra-esophageal GERD is complicated and not fully understood. There are a few most commonly accepted mechanisms to explain this complicated relationship (Figure 2). The pathophysiology of extra-esophageal symptoms includes predominately two proposed mechanisms: the reflux theory and the reflex theory.

Reflux theory

Reflux theory refers to direct retrograde reflux of gastric (acid and pepsin) and duodenal (bile acids and pancreatic enzyme trypsin) into the esophagus with subsequent aspiration into the lungs; or even higher up in the setting of dental erosions or laryngitis [3]. This leads to direct mucosal injury by gastroduodenal contents leading to extra-esophageal symptoms. Direct aspiration into lung tissue causes chronic inflammation, which can lead to impaired gas exchange and airway obstruction [21,22]. Symptom of regurgitation is a good marker for the possibility of reflux, especially if it occurs at nights while patients are in the supine position.

GER leads to the release of proinflammatory mediators such as T-helper type 2 cytokines, which increase airway resistance and airway inflammation [23,24]. Via direct hydrochloric intra-esophageal instillation, there is increased bronchoconstriction through muscarinic (M3) receptors, which release acetylcholine. This further contributes to airway inflammation and activation of airway smooth muscle contraction [25,26]. GERD-induced airway inflammation is histologically seen as infiltration of macrophages, neutrophils, eosinophils and lymphocytes. Multiple animal studies show the release of different interleukins increase release of TNF-α [27,28]. To determine the effect of acid in an *in vivo* human model, Mise *et al.* evaluated the impact of reflux on pulmonary physiology (n = 63) and found that in those with GERD, compared with normal controls, there was lower pH in the peripheral alveolar branches (pH of 5.13 vs 6.08, p = 0.001) and higher levels of LDH in

bronchoalveolar aspirates [29]. The increase in LDH is a marker of increased cell and tissue damage when pH is <6 *in vivo*, which reflects the direct damage of acid reflux in GERD.

The pathogenesis of GERD-induced asthma involves airway hyperresponsiveness, which ultimately is due to increased contractility of smooth muscles [30].

Reflex theory

The second pathophysiologic mechanism proposed is known as the reflex method and it operates on the principal that embryologically, the esophagus and bronchial tree share similar origin and neural innervation via the vagus nerve. With reflux, acidification of the distal esophagus can stimulate acid-sensitive receptors, which can lead to extra-esophageal symptoms [31]. Cheng *et al.* recently demonstrated that in a guinea pig model, direct acidification to the lower esophagus and subsequent micro-aspiration in the respiratory tract leads to airway hyperresponsiveness and overactive bronchial smooth muscles [32]. Donnelly *et al.* performed acid infusion in four subject groups in a blinded fashion: control, patients with GERD only, patients with asthma only and patients with GERD and asthma. They found that 72% of patients with GERD and asthma had increased respiratory resistance compared with 10% of patients with asthma alone [33].

High versus distal reflux

A further sub-classification symptom defines reflux as either 'high' or 'distal' esophageal reflux. In 'high' esophageal reflux, there is reflux traversing the esophagus and inducing cough by either direct pharyngeal/laryngeal stimulation or aspiration causing a tracheal or bronchial cough response [34]. In 'distal' esophageal reflux, vagally mediated tracheal-bronchial reflex induces cough [35,36]. Majority of patients with extra-esophageal symptoms do not exhibit increased proximal esophageal reflux when compared with patients with typical esophageal symptoms of GERD [37]. Many studies have also shown that in patients with GERD and asthma, there is an increase in esophageal dysmotility, which has also been shown in GERD patients with pulmonary aspiration and chronic cough [38–42].

Extra-esophageal GERD & pulmonary function

Studies in patients with GERD have shown direct changes in the patient pulmonary function status. Mirić*et al.* studied 71 children and compared pulmonary function testing in children with poor asthma control or chronic laryngitis with a medical history concerning for GERD (typical symptoms, hoarseness and weight gain) and evaluated the prevalence of GERD [43]. In the asthma group, 92.1% of children were found to have GERD on 24-h pH monitoring and when compared with the chronic laryngitis arm, they had worsened pulmonary flows as tested via peak expiratory flow (PEF) and maximal expiratory flow at 25, 50 and 75% [43]. Pirogowicz *et al.* studied 20 patients with GERD and chronic cough and showed a decrease in forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and maximal instantaneous forced expiratory flows compared with healthy individuals, which suggested that GERD itself can cause changes in pulmonary function independent of the formation of asthma [44].

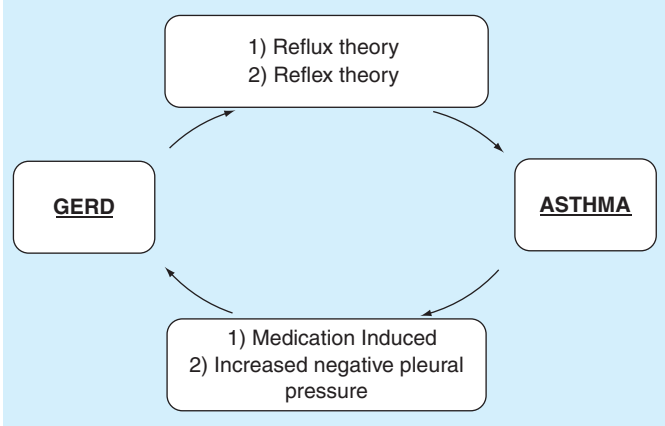

Figure 2. Relationship between GERD and asthma.
GERD: Gastroesophageal reflux disease.

Aras *et al.* showed that asthmatic patient with dysphagia were found to have significantly lower abnormal diffusion capacity of carbon monoxide (DLCO) and DLCO adjusted according to alveolar volume (DLCO/VA) [45]. In asthmatic patients, DLCO had been previously found to be normal or even high in asthmatics [46]. There is a lack of consensus on the relationship with severity of asthma and GERD. Where Aras *et al.* failed to show a relationship, Moayyedi and Axon showed that with increasing asthma severity there was a trend toward increased reflux (30% reflux in mild asthma, 76% reflux in moderate asthma and 70% reflux in severe asthma) [47].

Can asthma cause GERD?

Given the evidence of GERD leading to asthma, many authors have felt that asthma can lead to worsening GERD via two mechanisms: asthma medications and mechanical causes (Figure 2).

Asthma medications

Anti-asthmatic medications such as β-2-adrenergic receptor agonists or theophylline are proposed to relax smooth muscles including the lower esophageal sphincter (LES).

Ekstrom and Tibbling examined the use of theophylline and found a 24% increase in day-time reflux for those on theophylline with a 170% increase in symptoms of heartburn and regurgitation; notably, no LES measures were done in this study [48].

In 1991, Michoud *et al.* studied the β-2-adrenergic receptor agonist salbutamol at a dose of 4 mg per oral, which failed to change the LES pressure, severity of reflux symptoms or esophageal contraction pressure [49]. Furthermore, Zerbib *et al.* studied the role of bronchospasm versus salbutamol in altering the LES pressure. They found that in their group of patients with methacholine-induced bronchospasm, there was an increase in LES relaxation and increase in reflux episodes; however, in the group given salbutamol, there was a decrease in LES relaxation with no change in reflux events [50]. Hence, β-2-adrenergic

receptor agonists do not seem to relax LES pressure or lead to worsening GERD based on these studies.

However, one common anti-asthmatic medicine, prednisone, has been shown to increase esophageal acid in patients with stable asthma. Lazenby *et al.* performed a prospective, single-blinded, placebo-controlled crossover study with 20 adults with stable asthma and placed them on prednisone 60 mg/day for 7 days [51]. Using dual-probe esophageal pH monitoring, this group showed increased esophageal acid contact times at the distal and proximal pH probes after initiation of prednisone; however, they do note that in this small population there were no change in asthma or esophageal reflux symptoms.

Mechanical changes

The obstructive pattern of asthma leads to increased negative intrathoracic pleural pressure. This in turn leads to increased diaphragmatic pressure, which would favor the regurgitation of gastric content across the LES due to the pressure difference [6]. During asthma attacks, the negative intrathoracic pressure overcomes the protective effect of the LES and leads to reflux [52]. Many studies have also shown that asthmatics have lower LES pressure, making this gradient easier to overcome [53].

The interplay between asthma and GERD is complicated and many authors have looked at the biochemical changes to determine which factor is the inciting event. Zhu *et al.* set to determine if there was a physiological difference between asthma versus GERD-induced asthma [54]. In their study, they evaluated 60 rats with six arms: GER group, GER-associated asthma, allergic asthma and respective control groups. Through evaluation of bronchoalveolar lavage fluid, there was a higher concentration of IL-5 and eosinophils in allergic asthma compared with GER-associated asthma, which may be a potential method to distinguish these two processes [54]. The increase in eosinophils has been shown to increase asthma-associated airway inflammation and hyperresponsiveness, which does not appear to be acid-induced [55–58]. Similarly, Sacco *et al.* found that in GER-associated asthma, there was an increase in neutrophils compared with pH-negative children [59]. IL-13 has also been shown to be increased in GER-associated asthma [60]. Hence, there is a change in cytokines that may help determine the underlying etiology in this patient population.

Extra-esophageal GERD & asthma in children

GERD is common in children with asthma [61–64]. There have been few conflicting studies on the prevalence of asthma in GERD patients. In a study of International Classification of Diseases codes, the prevalence of asthma in children with GERD was 13.2% compared with just 6.8% in non-GERD controls [65]. Tsai *et al.* used endoscopy and 24-h pH monitoring and showed a twofold increased risk for developing asthma in patients with GERD [66]. However, both Ruigomez *et al.* and Ozcan *et al.* failed to show positive correlation with asthma and GERD [15,67]. In a study of 432 term infants, GERD is correlated with increased acute respiratory illness severity, but not with asthma diagnosed by age 4 [68]. Hence in children, there is an association with GERD and asthma, but no clear causation to date, though studies are limited.

Diagnostic consideration

A careful history and physical examination is important in evaluation of patients with asthma in whom GERD is suspected to play a role. Current diagnostic testing for reflux in patients with asthma has limitations due to sub-optimal sensitivity and/or specificity and often do not predict response to treatment (Table 1). The American College of Gastroenterology (ACG) guidelines suggest treatment with proton pump inhibitor (PPI) therapy for patients with extra-esophageal symptoms who also have typical symptoms of GERD [69]. Esophagogastroduodenoscopy is a common diagnostic test employed to assess for esophageal mucosal injury from GERD. For patients with asthma who are already on empiric PPI therapy, the likelihood of identifying esophagitis is low and is not recommended by the ACG guidelines as a means to establish the diagnosis of GERD-related asthma [69]. In a prospective cohort study, Kavitt *et al.* examined 75 patients both on and off PPI therapy and found that esophagitis was only present in 19% of their patients off PPI therapy and in this group 90% were grades A and B by Los Angeles Classification. None of their patients was found to have endoscopic evidence of Barrett's esophagus [70]. Even off PPI therapy, esophagogastroduodenoscopy has only 50% sensitivity and 70% specificity for diagnosing GERD [71]. Barium esophagram is helpful in diagnosing esophageal stricture or deep ulcers, but very insensitive in the diagnosis of GERD. Its utility for diagnosing esophagitis is also limited with sensitivities of 22% in mild esophagitis, 83% with moderate esophagitis and 95% with severe esophagitis [72].

Ambulatory esophageal pH monitoring has the highest sensitivity for the diagnosis of GERD (ranging from 88 to 95%) [73]. Esophageal pH monitoring is especially useful with atypical symptoms of GERD and allows the provider to determine the relationship of a patient's reflux with their symptoms. Although there are limitations to pH testing, this monitoring offers a possible diagnostic test that can be performed on treatment to determine extent of effect on acid suppression with patient's with refractory symptoms on therapy. Esophageal manometry is an insensitive test for the diagnosis of GERD. Richter studied the utility of manometry and showed that a low LES pressure <10 mmHg had the best specificity (84%) with poor sensitivity (58%) [74].

Impedance monitoring, which can measure any physiological reflux regardless of pH can detect the frequency, location and direction of any gas or liquid that is refluxed into the esophagus. Unlike traditional dual-channel pH probe testing that only reports acidic changes in the esophagus, impedance monitoring can determine the presence of any remaining physiologic reflux regardless of pH. Although initial support, outcome studies with this device are lacking and the clinical relevance of impedance findings in laryngopharyngeal reflux (LPR) patients who continue to have symptoms despite PPI therapy still remains uncertain [75–77]. In one study evaluating 41 patients diagnosed

Table 1. Advantages and disadvantages of methods for detecting esophageal reflux.

Method	Advantages	Disadvantages
Endoscopy	• Easy visualization of mucosal damage/erosions	• Poor sensitivity/specificity/PPV • Requires sedation • High cost
pH monitoring	• Easy to perform • Relatively non-invasive • Prolonged monitoring • Ambulatory	• Many are catheter-based • May have up to 30% false-negative rate • No pH predictors of treatment response in LPR
Impedance monitoring	• Easy to perform • Relatively non-invasive • Prolonged monitoring • Ambulatory • Measures acidic and non-acidic gas and liquid reflux (combined with pH)	• Catheter based • False-negative rate unknown but most likely similar to catheter-based pH monitoring • Unknown clinical relevance when abnormal on PPI therapy
Reflux symptom association assessment	• Correlate pH values with pathological symptoms • Values can correlate with PPI responsiveness	• Subjective scoring
ResTech Dx-pH	• Faster detection rate and faster time to equilibrium pH than traditional pH catheters	• Inconsistencies with impedance monitoring
Lateral flow device for pepsin	• Fast and easy detection of salivary pepsin • Acceptable sensitivity and specificity	• Limited outcome studies

LPR: Laryngopharyngeal reflux; PPI: Proton pump inhibitor; PPV: Positive predictive value.

with LPR by reflux finding score and reflux symptom index (SI), impedance monitoring confirmed GERD diagnosis in less than 40% of patients, which was felt due to the low specificity of laryngoscopic findings, which supports the utility of impedance in determining the association between GERD and LPR [78]. Hence, pH monitoring off PPI therapy can be used to provide baseline esophageal reflux parameters. Impedance monitoring (if entertained) may be used on PPI therapy and should be reserved for those who continue to have symptoms despite acid suppressive therapy. In patients with chronic cough, pathological acid exposure time or impedance baseline increases the sensitivity of impedance testing in determining which patients respond to PPI with typical GERD symptoms [79]. However, in general, impedance monitoring findings alone should not be used to determine the need for surgical fundoplication.

Oropharyngeal pH monitoring (ResTech pH) is another modality to measure reflux via a nasopharyngeal catheter to measure pH in either liquid or aerosolized droplets. A comparison of this device to the traditional pH catheters has shown faster detection rate and faster time to equilibrium pH [80]. One prospective observational study in healthy volunteers developed normative data for this device at pH cutoff of 4, 5 and 6 for the distal esophagus and oropharynx [81]. Significantly higher number of reflux events has been detected by Restech pH in LPR patients than patients with GERD and healthy volunteers concluding that the device may hold promise in evaluation of those with suspected GERD related LPR [80,82]. From a surgical standpoint, an abnormal Restech pH was associated with 90% of patients who have extra-esophageal GERD symptoms that were improved with antireflux surgery; whereas a negative Restech study more reliably indicated the absence of reflux-induced extra-esophageal symptoms [83]. Many studies have compared Restech pH with concurrent esophageal pH monitoring or impedance monitoring and have inconsistencies ranging from the oropharyngeal probe registering lower pH values during sleep and higher rate of false-positive and non-correlating pharyngeal events [84–86]. Thus, further controlled outcome-driven studies are needed to assess the future role of this new device in this difficult-to-diagnose and manage group of patients.

Ambulatory pH monitoring can be combined with symptom-reflux indices to help determine if low pH values are causing pathological signs of GERD. Tools to quantify the relationship between symptoms and reflux include the SI, Symptom Sensitivity Index (SSI), Symptom Association Probability (SAP) and Binomial Symptom Index. Studies evaluating the reproducibility showed the percentage of patients with similar outcomes on consecutive days for SI, SSI and SAP to be 67, 86 and 86%, respectively [87,88]. Positive SI, SSI and SAP have been positively correlated with response to therapy further validating this model [89,90]. However, a recent study by Slaughter *et al.* concluded that both SI and SAP indices can be overinterpreted and are prone to misinterpretation [91]. They suggested that unless patients with GERD have high rates of esophageal acid exposure, both SI and SAP indices are essentially chance occurrences at best. Furthermore, employing ambulatory acoustic monitoring it was recently reported that up to 71–91% of patients do not accurately report their cough events, which further reduces the enthusiasm on the use of

symptom indices in pH monitoring [92]. Thus, given low predictive value of pH testing, lack of reliability of SAP and temporal association, which may not be causal, pH testing in patients with chronic cough or asthma may be misleading.

Measuring salivary pepsin has also been used in the detection of GERD, especially in reflux-related laryngitis. Using an enzymatic method, Potluri *et al.* compared salivary pepsin activity with proximal and distal esophageal pH results in 16 reflux patients and found that the mean proximal and distal pH values correlated with salivary pepsin assay findings [93]. The authors concluded that salivary pepsin assay might be a non-invasive method to assess for proximal reflux. While, Ozmen *et al.* found 100% sensitivity and 92.3% specificity for pepsin assay in nasal lavage fluid in chronic rhinosinusitis patients [94], Printza *et al.* did not demonstrate any peptic activity in 93 LPR patients' saliva samples [95]. Employing western blot technique for sputum and salivary pepsin samples in patients with extra-esophageal reflux, Kim *et al.* reported sensitivity and specificity of 89 and 68%, respectively based on the pH monitoring results [96]. A novel pepsin rapid test (Peptest-Biomed) is also being used as a convenient, office-based, non-invasive, quick and inexpensive technique in LPR diagnosis. In a prospective, blinded study of salivary pepsin assay in 58 patients with objective GERD (esophagitis or abnormal pH testing) compared with 51 controls subjects, there was a positive and negative predictive values of 87 and 78%, respectively [97]. The sensitivity and specificity of the assay was 87% by *in vitro* bench testing; pepsin was positive in 12% of controls and in 22% in patients with GERD with the highest levels of pepsin correlating with endoscopy esophagitis. This was complemented by Hayat *et al.*, who studied 100 asymptomatic controls and 111 patients with heartburn and tested the utility of the salivary pepsin test and found elevated pepsin in GERD and in hypersensitive esophagus; when using a value of >210 ng/ml pepsin, there was a 98.2% specificity and likelihood ratio of 25.1 [98]. However, the role of salivary pepsin in diagnosing reflux in patients with asthma is currently uncertain and awaits further trials.

Treatment

Histamine receptor antagonist

Many studies have assessed the utility of histamine (H-2) receptor antagonist in the treatment of GERD and its overall improvement in asthma symptoms (Table 2). Multiple studies have shown improvement with H-2 receptor antagonist versus placebo in regards to nocturnal asthma symptoms and objective pulmonary function [99–101]. In a unique double-blind placebo-controlled study comparing H-2 receptor antagonist, surgery and placebo, Larrain *et al.* randomized 90 patients to either cimetidine 300 mg four-times a day, antireflux surgery (modified posterior gastropexy) or placebo for 6 months with both cimetidine and surgery arms showing statistically significant improvement in symptoms, FEV_1 and expiratory flows compared with placebo [102]. Not all studies have shown improvement of symptoms, but these double-blind placebo studies were limited in population (primary age group was adolescents) and in length of therapy (as short as 7 days of treatment) [103,104]. Hence, for histamine receptor antagonist, there was improvement in subjective asthma symptoms with an overall trend toward improvement in pulmonary function in the adult population with a minimum of 4 weeks of treatment.

Proton pump inhibitor

PPIs are the most effective treatment for GERD. With the positive findings from histamine-receptor antagonist and the improved acid suppression with PPIs, many trials are conducted to determine the effect of PPIs on asthma symptoms and PFTs (Table 3). For example, Shimizu *et al.* performed a randomized prospective trial comparing lansoprazole, roxatidine and placebo and showed improvement in PEF and asthma symptoms with only lansoprazole but not with roxatidine, although neither had any change in FEV_1 [105]. Multiple studies have shown improvement on asthma symptoms with PPI therapy [106–109]. Kiljander *et al.* performed a double-blind, placebo-controlled crossover study evaluating the use of omeprazole 40 mg once a day (q.d.) versus placebo for 8 weeks with a 2-week washout period, which showed a reduction in nocturnal asthma symptoms with the best improvement in patients with severe distal esophageal reflux and obese patients [20,110]. This was supported further in a placebo-controlled study, where Kiljander *et al.* treated asthma patients aggressively with esomeprazole 40 mg twice a day (b.i.d.) for 4 months and showed that esomeprazole improved PEF in subjects with asthma and when compared with b.i.d. versus q.d. dosing, only b.i.d. dosing showed improvement in FEV_1 [111,112]. In support of b.i.d. dosing, Meier *et al.* examined the use of omeprazole 20 mg b.i.d. in a double-blinded placebo-controlled study and showed that 27% of asthmatics had >20% improvement in FEV_1 after 6 weeks of treatment [113]. Peterson *et al.* examined the role of rabeprazole 20 mg q.d. versus 20 mg b.i.d. versus placebo in patients with exercise-induced asthma and showed improvement of exercise-related symptoms for those on a PPI, but no difference in q.d. dosing, although their study was limited by using a lower dose of PPI compared with prior studies and points to exercise-induced asthma as having a different physiology than GERD-associated asthma [114].

However, not all studies have shown improvement in asthma symptoms with PPIs. In a population most similar to the aforementioned studies, Littner *et al.* followed 207 patients with moderate-to-severe asthma and symptomatic reflux, who were treated with either placebo or a PPI b.i.d. for 24 weeks and showed that medical treatment did not reduce daily asthma symptoms, but did reduce asthma exacerbation and improved asthma-related quality of life [115]. The American Lung Association Asthma Clinical Research Center randomized 412 patients with poor asthma control without symptomatic reflux to either esomeprazole 40 mg b.i.d. or placebo and after 24 weeks, which found no treatment benefit of PPI therapy in asthma control, although these patients already had inadequate asthma control despite inhaled corticosteroids [116]. Multiple other studies comparing poorly controlled asthmatic children have

Table 2. Notable studies comparing effects of histamine receptor antagonists on asthma control.

Study (year)	Study type	Patients	Medication	Dose	Length of study	Outcome	Ref.
Goodall *et al.* (1981)	Double-blind placebo controlled crossover	18	Cimetidine	200 mg q.d.	6 weeks, then crossover, no washout	Improvement in nocturnal asthma symptoms and peak flow	[99]
Harper *et al.* (1987)	Prospective study	15	Ranitidine	150 mg b.i.d.	8 weeks	Improvement in asthma symptoms and pulmonary function	[100]
Nagel *et al.* (1988)	Double-blind placebo controlled crossover	15	Ranitidine	150 mg qam, 300 mg qpm	7 days, then 3-day washout	No improvement in asthma symptoms or PEF	[104]
Ekstrom *et al.* (1989)	Double-blind, placebo controlled	48	Ranitidine	150 mg b.i.d.	4 weeks	Improvements in nocturnal asthma and use of bronchodilators, no change in lung function or peak flow	[101]
Larrain *et al.* (1991)	Double-blind placebo controlled	90	Cimetidine	300 mg q.i.d.	6 months, also included surgical arm	Improvement in asthma symptoms in both medical and surgical arm compared with placebo	[102]
Gustaffson *et al.* (1992)	Double-blind, placebo controlled	37	Ranitidine	300 mg b.i.d.	4 weeks	In children, reduction of nocturnal asthma symptoms	[103]
Sontag *et al.* (2003)	Randomized controlled trial	62	Ranitidine	150 mg t.i.d.	Three arms: ranitidine, Nissen and placebo	Only Nissen improved asthma symptoms; no change with ranitidine; neither effected pulmonary function	[121]

b.i.d.: Twice a day; q.i.d.: Four times a day; t.i.d.: Three times a day.

also been negative, which is similar to the findings in H-2 receptor antagonist in children [117,118].

Other studies with negative findings were limited by small population size, inadequate dosing (20 mg PPI q.d.) and inclusion of patients with chronic obstructive pulmonary disease, which is a different entity than GERD-associated asthma [119,120]. In summary, patients with poorly controlled asthma despite corticosteroid without symptoms of reflux and children do not respond to aggressive PPI therapy, which is likely due to the lack of GERD contributing to their symptoms. However, in patients with symptomatic reflux, there is still improvement in asthma exacerbations in addition to pulmonary function. Most experts agree on empiric trial of PPI if GERD is suspected as a contributing factor to patients' continued asthma exacerbations.

Surgery

The ACG guidelines report that surgery should typically not be performed in patients with extra-esophageal GERD who do not respond to appropriate acid suppression with PPI [69]. To determine the utility of surgical management, Sontag *et al.* evaluated 62 patients with both GER and asthma and divided the group into three treatment arms: control, treatment of reflux with ranitidine 150 mg three-times a day or surgical treatment with Nissen fundoplication [121]. After a 2-year follow-up, 75% of surgical patients had improvement in nocturnal asthma exacerbations, compared with 9.1 and 4.2% of patients on medical therapy and controls, respectively. Multiple studies have shown improvement in asthma symptoms after Nissen fundoplication [122–124]. Ozaydin *et al.* studied 40 patients with GERD and asthma with the intent to study the differences between pre- and post-laparoscopic Nissen fundoplication. They found a statistically significant increase in FVC, FEV_1/FVC and forced expiratory flow between 25 and 75% of vital capacity; they did no see a change in FEV_1 [125]. This study was limited by the total number of patients and single-centered study, which may limit its generalizability.

Table 3. Notable studies comparing effects of proton pump inhibitor on asthma control.

Study (year)	Study type	Patients	Medication	Dose	Length of study	Outcome	Ref.
Ford *et al.* (1994)	Placebo-controlled crossover	11	Omeprazole	20 mg q.d.	4 weeks treatment, 1 week run-in and crossover periods	No changes in symptoms or PEF	[119]
Meier *et al.* (1994)	Double-blind, placebo controlled	15	Omeprazole	20 mg b.i.d.	6 weeks	Improvement in FEV_1 by >20%	[113]
Harding *et al.* (1996)	Prospective study	30	Omeprazole	20 mg q.d.	3 months	Improvement in asthma symptoms and/or PEFs by >20%; improved pulmonary function in 73% of patients	[106]
Boeree *et al.* (1998)	Double-blind placebo controlled	36	Omeprazole	40 mg b.i.d.	12 weeks, no crossover	No changes in asthma symptoms or PEF. *Included patients with COPD	[120]
Levin *et al.* (1998)	Double-blind placebo controlled crossover	9	Omeprazole	20 mg q.d.	8 weeks, no washout, then crossover	Improvement in PEF and subjective asthma symptoms	[108]
Kiljander *et al.* (1999)	Double-blind placebo controlled crossover	107	Omeprazole	40 mg q.d.	8 weeks of treatment, 2 weeks washout, then crossover	Reduction of nocturnal asthma symptoms, no change in daytime asthma symptoms	[20]
Kiljander *et al.* (2001)	Double-blind placebo controlled crossover	52	Omeprazole	40 mg q.d.	8 weeks, 2-week washout, then crossover	Improvement in asthma symptoms by >20% in 35% of patients	[110]
Littner *et al.* (2005)	Multicenter, double-blind, randomized, placebo-controlled trial	207	Lansoprazole	30 mg b.i.d.	24 weeks	No improvement in asthma, although improvement in number of exacerbations and in quality of life	[115]
Stordal *et al.* (2005)	Randomized controlled trial	38	Omeprazole	20 mg q.d.	12 weeks	In children, no improvement in asthma symptoms or pulmonary function	[118]
Kiljander *et al.* (2006)	Multicenter, double-blind, randomized, placebo-controlled	770	Esomeprazole	40 mg b.i.d.	16 weeks	Improvement in PEF with nocturnal symptoms, no improvement in PEF	[111]
Shimizu *et al.* (2006)	Randomized controlled trial	45	Lansoprazole, ranitidine	30 mg/day; 150 mg/day	2 months	Lansoprazole improved asthma symptoms and PEF; no change in FEV_1	[105]
Peterson *et al.* (2009)	Randomized double-blind controlled trial	31	Rabeprazole	20 mg q.d. or 20 mg b.i.d.	12 weeks	Improved symptoms of exercise-triggered asthma	[114]
Kiljander *et al.* (2010)	Double-blind placebo controlled crossover	961	Esomeprazole	40 mg q.d. or b.i.d.	26 weeks	Improvement in FEV_1 and asthma symptoms; no difference between q.d. and b.i.d. dosing	[112]
American Lung Association (2012)	Randomized double-blind controlled trial	306	Lansoprazole	15–30 mg q.d. (weight based)	24 weeks	In children, no improvement in asthma symptoms or pulmonary function; increased adverse events	[116]

b.i.d.: Twice a day; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in 1 s; PEF: Peak expiratory flow; q.d.: Once a day.

Nissen fundoplication has been well studied in typical GERD with success rates reported as 90% at 10 years [126]. Other reviews have reported that the Toupet fundoplication has less post-operative dysphagia, bloating and reoperation rate [127]. Koch *et al.* performed a randomized prospective study examining the role of laparoscopic total (Nissen) and partial (Toupet) fundoplication in 100 patients with extra-esophageal GERD, where Toupet fundoplication failed to improve asthma symptoms [128]. To further elucidate who would benefit from Nissen fundoplication, Francis *et al.* performed a retrospective cohort study and found that patients with both heartburn with or without regurgitation and esophageal pH <4 more than 12% of a 24-h period were predictive of post-fundoplication resolution of the presenting extra-esophageal reflux symptom [129]. Hence, surgical fundoplication may be useful in select patients who continue to have regurgitation despite PPI therapy, have moderate-to-severe reflux measured by pH monitoring off therapy and who might have mechanical defect such as a moderate-sized hiatal hernia (>4 cm). Otherwise, we do not recommend surgery just because patients continue to have worsening asthma who have minimal reflux by objective testing.

Treatment recommendations

For typical GERD, the ACG guidelines recommend an 8-week course of PPIs as the first-line therapy for symptom treatment and healing of erosive esophagitis [69]. The current recommendation in patients with GERD-related asthma (with or without concomitant heartburn or regurgitation) is similar to those in patients with chronic cough and laryngitis, suggesting the initial empiric trial of b.i.d. PPIs for 6–8 weeks, where the recommendation for extra-esophageal GERD treatment is 4–8 weeks (Figure 3). This duration is based on the aforementioned studies where inadequate treatment time (as low as 4 weeks) had negative findings, where studies with at least 8 weeks of treatment were able to show a signal for response. In an effort to reduce cost of unnecessary PPI treatment, this duration allows the provider to determine if there will be a response in treatment. As discussed above, patients with poorly controlled asthma despite maximal corticosteroids without symptoms of reflux and children have classically not responded to empiric PPI trial; these patients should be discussed individually to determine if a PPI trial is indicated. In those responsive to therapy for both heartburn and/or asthma symptoms, PPIs should be tapered to the minimal dose necessary to control symptoms. ACG guidelines state that patients treated with PPI who do not respond in 2–3 months should be considered refractory GERD [69]. Surgical fundoplication should be reserved for patients with moderate-to-severe reflux parameters at baseline, moderate-sized (>4 cm) hiatal hernia and concomitant heartburn and/or regurgitation. Surgical fundoplication is not recommended for patients who are unresponsive to aggressive medical treatment. In unresponsive patients, testing for reflux, by pH testing and/or impedance-pH monitoring may be needed to measure for continued reflux of acid or non-acid material, which could still be responsible for patients' asthma exacerbation. In most, reflux is not contributing and a search for other potential triggers must ensue.

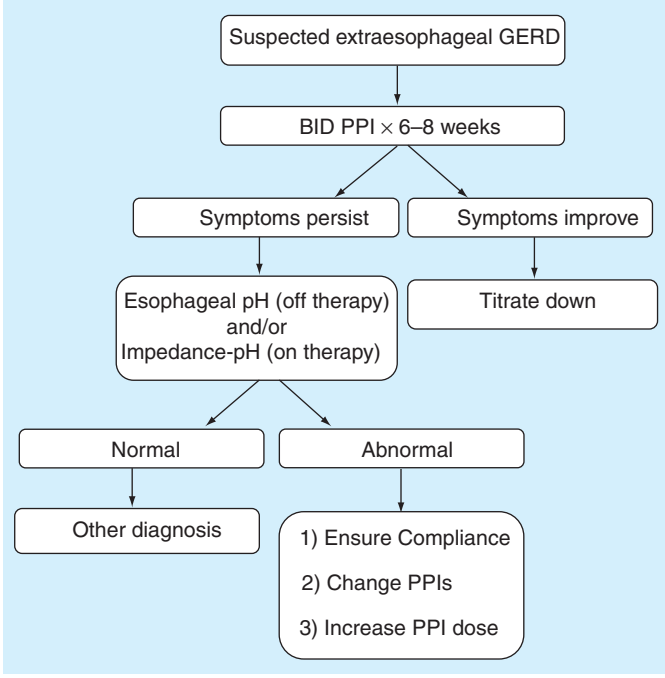

Figure 3. Treatment algorithm for GERD-induced asthma.
GERD: Gastroesophageal reflux disease.

Conclusions

The relationship between extra-esophageal GERD and asthma is both complicated and incompletely fully understood. There is likely a continued cycle of symptom development after the initial insult, although diagnosing the initial insult, despite being an immerging field, is still not exact. The complexity of patient presentation is matched by the challenge in appropriate diagnosis of reflux as the cause for the patient complaints. Whether utilizing upper endoscopy or pH monitoring, diagnostic tests suffer from either poor sensitivity and/or poor specificity, which most importantly has yet to be linearly related to a patient's response rate. Thus, acid suppression with PPI therapy is typically the first-line choice of diagnosis as well as therapy. For those who improve with PPIs, GERD is presumed to be the etiology, but for those who do not respond, diagnostic testing with impedance and/or pH monitoring are reasonable to typically exclude continued acid or weakly acid reflux. Extra-esophageal symptoms are known to be multifactorial and hence isolated acid suppression may not always suppress these symptoms relegating these causes as non-GERD related. Surgical fundoplication should not be considered in patients who are unresponsive to aggressive PPI therapy but may be reasonable in those with moderate-to-severe acid reflux, large hiatal hernia and regurgitation despite PPI therapy in whom volume reflux may be the cause for patients' continued symptoms. Further studies are needed to determine the exact mechanism of this disease process and better stratify which patient populations, whether it be through pulmonary function testing, symptom scores or age, to determine dose and duration of therapy.

Expert commentary & five-year view

GERD-associated asthma is a difficult entity to treat and diagnose due to the complex etiologies that lead to asthma. The interplay between asthma and GERD is incompletely understood, but important to research as the pathophysiology of these disease states determines appropriate treatment. With increasing amounts of animal and human models to determine this interplay, much has been learned on the direct effect of reflux in the lungs and the interaction of intrathoracic pressure on the development of GERD. Further studies are needed to determine correct causality in order to determine correct intervention for treatment. Through continued clinical studies, including randomized double-blinded, placebo-controlled, crossover trials, we hope to have definitive treatment option, dosage and therapy; which will likely be catered based on age group and demographics. Future trials should focus on preplanned subgroup analysis to determine how the severity of asthma via pulmonary function and objective symptoms are improved with varying doses and durations of PPI therapy. Furthermore, there is a paucity of literature on the long-term follow-up with guidelines on long-term PPI therapy and appropriate weaning strategies once treatment is commenced. Earlier recognition of extra-esophageal GERD and asthma will lead to targeted therapy of high-risk patients with hopeful stratification of dosage and duration of therapy based on quantitative diagnostic criteria. Given this interplay, accurate history and physical examination is important as empiric treatment with b.i.d. PPI is appropriate for concerns for extra-esophageal GERD. However, the role of non-acidic reflux in asthma is poorly understood and is an important subgroup of patients to target as these are often non-responders to PPI treatment and alternative modalities for diagnosis (whether via impedance monitoring) and treatment are not fully delineated. Increased attention will be placed on efficient diagnosis and treatment to improve patient care and decrease economic burden of this particularly difficult entity.

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Key issues

- Asthma and extra-esophageal gastroesophageal reflux disease (GERD) are increasing in incidence with high economic burden.
- Extra-esophageal GERD can cause asthma through the reflux and reflex models.
- Asthma induces mechanistic and physiological changes, which can also lead to GERD.
- Cytokine release, including the release of TNF-α is important to both models, although the exact mechanism of its effect has yet to be elucidated.
- Lack of optimal sensitivity and specificity of current diagnostic testing, such as upper endoscopy, pH monitoring and impedance monitoring, makes diagnosis particularly difficult.
- There is a lack of a predictive model to determine which patients will benefit from therapy.
- Current paradigm includes empiric therapy with high dose, twice a day dosing of proton pump inhibitor.
- There have been several conflicting studies on treatment dose, duration and utility; further studies still needed to help determine the ideal population for treatment with highest success rates of treatment.

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