Gastro-esophageal reflux disease and poorly controlled asthma in pediatric population: are they linked? Effect of anti-reflux treatment

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Abstract

Gastro-esophageal reflux disease GERD is the backward flow of stomach acids into the esophagus. When this acid enters the lower part of the esophagus, it can produce a burning sensation, commonly referred to as heartburn. (GERD) is the most common esophageal disorder in children. It causes various pulmonary manifestations and bronchial asthma is one of them. The relationship between GERD and pulmonary manifestations is quite challenging and ongoing research efforts have focused on the elucidation of the pathogenesis of GERD induced asthma.

The aim of this article is to assess the prevalence of GERD in a group of moderate persistent or severe persistent asthma and to evaluate the clinical response of asthma to anti-reflux treatment.

Methods: Using internet search, a comprehensive literature review was done and words such as Bronchial asthma, gastro esophageal reflux disease, Asthma; Proton pump inhibitors; were searched.

The references of the relevant articles on this subject were also searched for further information.

Results: Analyses of results of various studies from various parts of the world were considered and their prevalence was noted to access the correlation between asthma and GERD.

Conclusion: The results of review research indicate a relationship between gastroesophageal reflux and asthma, patients with persistent asthma should be screened for reflux and receive treatment for better control of their asthma.

Key words: Gastro-esophageal reflux disease, asthma, pediatric population, anti-reflux treatment

Introduction

Gastroesophageal reflux, defined as the passage of gastric contents into the esophagus, is distinguished from gastroesophageal reflux disease (GERD), which includes troublesome symptoms or complications associated with GER [1]. Differentiating between GER and GERD lies at the crux of the guidelines jointly developed by (NASPGHAN) / (ESPGHAN) [1]. Therefore, it is important that all practitioners who treat children with reflux-related disorders are able to identify and distinguish those children with GERD, who may benefit from further evaluation and treatment, from those with simple GER, in whom conservative recommendations are more appropriate. Studies on normal infants demonstrated episodes of reflux as much as 73 times per day [2]. Infant reflux becomes evident in the first few months of life, peaks at 4 months old and disappears in up to 88% by 12 months old and almost completely by 24 months old [3]. About 60% of children with asthma have concomitant gastroesophageal reflux disease (GERD)[4] . In children, GER can present with respiratory manifestations for example chronic coughing, asthma, laryngeal spasm, apnea, stridor, pulmonary dysplasia. Nocturnal wheezing or coughing, with inadequate response to medical treatment for asthma, negative family history of atopia and early onset of bronchial hyper-reactivity characterize patients who should be studied for GER and wheezing can be the only manifestation of reflux in some children, indicating occult GER[5]. The prevalence of symptoms of GERD among individuals with asthma is substantially higher than in the normal population and similarly the prevalence of asthma in individuals with GER is also higher than in controls [6]. Gastroesophageal reflux (GER) may cause chronic respiratory disease by vagal response and tracheal aspiration of gastric contents [7]. Aspiration of gastric contents changes pulmonary resistance and causes reactive airway obstruction. Although older studies from the 1990s suggested that GERD may aggravate asthma, recent publications have suggested that the impact of GERD on asthma control is considerably less than previously thought [8].

The prevalence of GERD is higher in children suffering from obesity, neurological diseases, congenital heart disease, gastrointestinal tract abnormalities, congenital diaphragmatic hernia, and chromosomal abnormalities; also obesity is known to be a risk factor for increased reflux. Respiratory complications of GERD are common in the pediatric population, asthma being the most widely studied and whose occurrence is mainly attributed to vagal mechanisms, neurogenic inflammation, acid micro aspiration, and increased bronchial reactivity [8]. Furthermore, gastroesophageal reflux may contribute to airway inflammatory events, possibly by sensory nerve stimulation and the subsequent release of tachykinins into the airway [7]. A review of recent studies concerned the treatment of GER in asthmatics, both with pharmacological and surgical methods. Beneficial effect of anti reflux therapy on the course of asthma has been emphasized [9]. In addition, because GERD is a common condition, particularly in young children, the role reflux plays in the worsening of asthma symptoms and the potential benefit on asthma of anti-reflux therapy warrants further exploration[10]. Furthermore, medical treatment of asthma has been implicated in the pathogenesis of GERD especially theophylline has been implicated in an increase in gastric acid secretion and in a decrease of lower gastroesophageal sphincter pressure, enabling the appearance of GERD[11].

Pathophysiology of GERD-induced Asthma

Several proposed mechanisms about the pathophysiology of GERD-induced asthma exist, although these mechanisms are not completely understood. Proposed mechanisms of GERD-induced asthma include a vagally mediated reflex, heightened bronchial reactivity, micro aspiration and immune system modification. The pathways of some esophageal and airway sensory nerves terminate in the same regions of the CNS. It appears possible that synergistic interactions between esophageal nociceptors and airway sensory nerves may precipitate the asthma-like symptoms associated with GERD [12]. The esophagus and bronchial tree share embryonic origins and innervation through the vagus nerve; therefore, acid in the esophagus could stimulate esophageal receptors, initiating a vagally mediated reflex [13]. Many studies show that the vagally mediated reflex mechanism is important to GERD-induced bronchoconstriction, while others report conflicting data. Mansfield and Stein showed that patients with reflux had a 10% increase in airway flow resistance [14]. Wright et al measured airflow and arterial oxygen saturation before and after esophageal acid infusions in 136 individuals [15]. Measurements of airway flow, arterial oxygen saturation, and pulse rate were performed before and after intraesophageal infusion of sterile water, normal saline solution, and 0.1 N hydrochloric acid. Highly significant reductions in heart rate, airway flow, and arterial oxygen saturation were noted after infusion of normal saline and 0.1 N hydrochloric acid compared with baseline water infusion. It is concluded that acid-induced, vagally mediated esophagobronchial reflexes are present in humans [15]. Intraesophageal acid infusions caused a decrease in PEF in all groups without evidence of micro aspiration, implying a vagally mediated reflex may be involved [16]. Field analyzed 18 studies that reviewed the effects of GERD on pulmonary function in adults with asthma [17]. He concluded that the effects of esophageal acid on pulmonary function are minimal and only affect a minority of subjects. Another proposed mechanism of GERD-induced asthma is heightened bronchial reactivity. Herve et al[18] analyzed the effect of esophageal acid infusion on expiratory flow using voluntary isocapnic hyperventilation of dry air and methacholine challenge tests in asthmatics with and without GERD. The total dose of methacholine required to reduce the FEV1 by 20% was significantly lower when esophageal acid was infused vs normal saline solution[18]. Some data suggest that exposure to esophageal acid may increase bronchial activity to other stimuli. Perfusion of acid into the distal esophagus caused slight but significant

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In addition, increased gastroesophageal reflux and impaired function of the upper esophageal sphincter may contribute to more transpharyngeal spray and micro-aspiration, in turn leading to airway irritation, inflammation and hyper-responsiveness, which may cause or increase the severity of asthma [23].

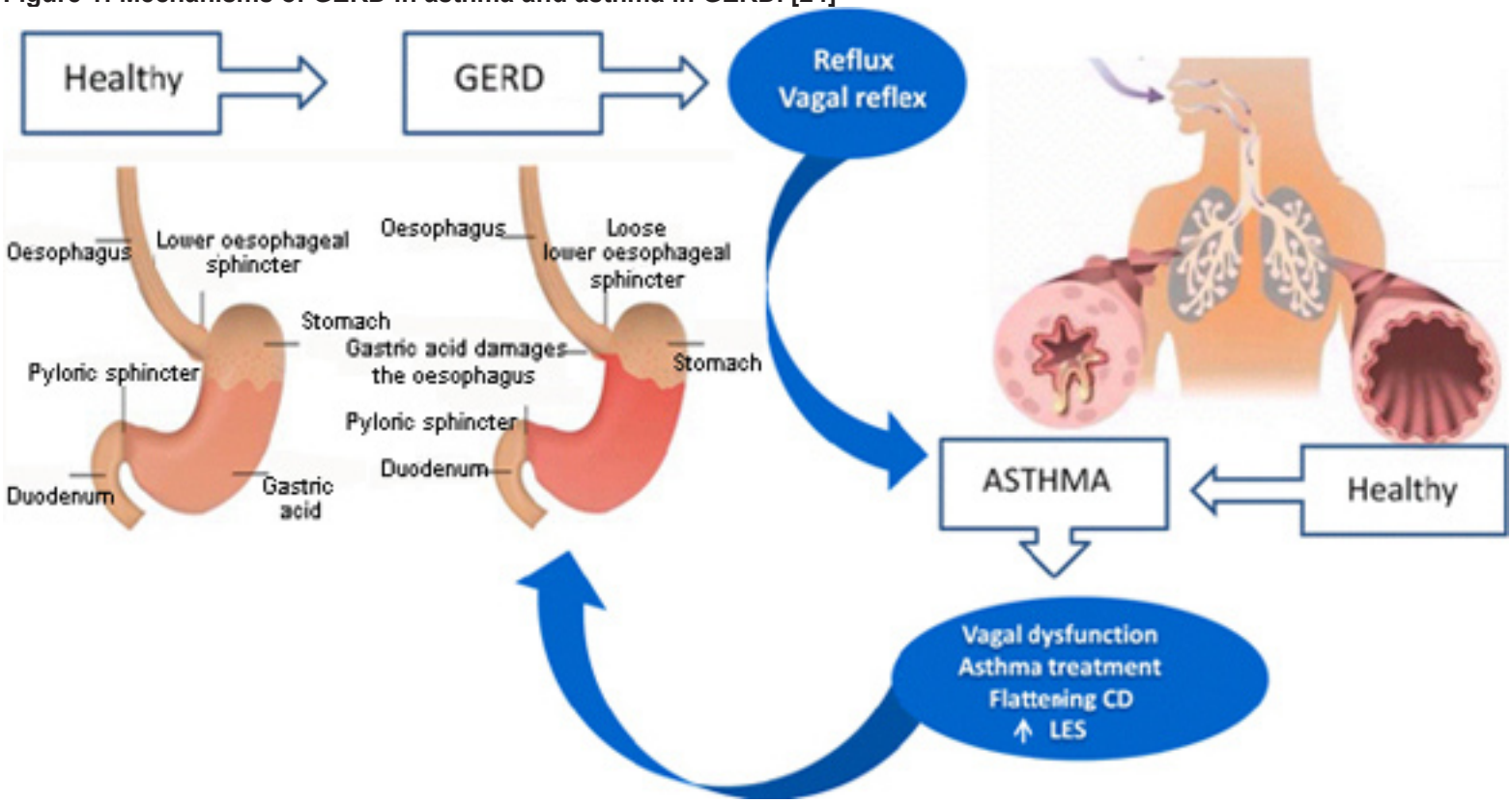
A recent study conducted at Duke University showed that GERD may alter the immune system's response to allergens, further strengthening the link between GERD and asthma [20]. Chronic aspiration has a profound effect on the nature of the immune response to aerosolized allergens in a model of experimentally induced airway hypersensitivity. The comparison group's response was more balanced, releasing both type 1 and type 2 helper T cells. This study shows that microaspiration may lead the immune system to generate an asthmatic response [21].

The prevalence of GERD in asthmatic patients

The association of asthma with gastroesophageal reflux disease has attracted particular attention because many patients with asthma have GERD. The prevalence of asthma has increased; however, the number of patients who die from it has decreased (1.3 per 100,000 patients in 2018) [25]. In the United States, an estimated 20 million people have asthma, and almost 20% of the U.S population suffers from the classic symptoms of GERD, such as heartburn and regurgitation, at least once a week [26]. Some studies have reported a higher prevalence of asthma among obese individuals [27]. Thus, obesity may be a strong predisposing factor for both GERD and asthma and a risk factor for both conditions.

Gastro-esophageal reflux is commonly noted in asthmatics, with a reported incidence of up to 60% in children with moderate-to-severe asthma [28]. It has been implicated as a cause of asthma exacerbations and increasing asthma symptoms. It was reported that GERD was diagnosed in 75% of children with chronic asthma who were refractory to medical treatment [29]. In a study for GERD in preschool children they found that (66.7%) had positive results (GERD positive group), in (80%) who underwent GERD therapy (famotidine), respiratory symptoms were decreased. In those patients the incidence of acid reflux during waking hours was more frequent than during sleeping hours [30]. Mays,[31] using a barium esophagogram, found that 13 of 28 (46%) asthmatics had evidence of reflux vs 23 of 468 (5%) normal control subjects.

Figure 1: Mechanisms of GERD in asthma and asthma in GERD. [24]



More recently Sontag et al [32] evaluated 186 consecutive adult asthmatics with endoscopy and esophageal biopsy and found that 79 (43%) had evidence of esophagitis or Barrett's esophagus. Among the 109 patients with asthma who participated in the study, 77% experienced heartburn and 55% experienced regurgitation; symptoms were higher than in the control groups. O'Connell et al also utilized a symptom survey to examine prevalence of GERD in 189 patients with asthma in a Veterans Administration (VA) hospital [33]. Seventy-two percent of the patients reported heartburn. A study by Chipps BE, Haselkorn found that a total of 341 (27.7%) patients were enrolled in TENOR II and were representative of the TENOR I cohort. The most frequent comorbidities were rhinitis (84.0%), sinusitis (47.8%), and gastroesophageal reflux disease (46.3%) [34]. These results suggest that the prevalence of GERD symptoms in patients with asthma is increased; however, it does not establish causality. However, as in the chronic cough population, some asthmatics may have significant GERD without classic reflux symptoms. Irwin et al [35] reported that GERD was clinically "silent" in 24% of asthmatics. So it would make sense to treat any concomitant gastro-esophageal reflux in patients with difficult severe asthma, but larger trials are needed to establish the value of this treatment in the poorly asthma patient.

Asthma as respiratory disease

Childhood asthma is not a singular disease, but rather a uniquely diverse disorder with variable presentation throughout childhood. Asthma affects 8.3% of children in the United States and is the most common chronic disease of childhood [36]. Three phenotypes have been identified in children with asthma: transient wheezing, non-atopic wheezing of the toddler and pre-school-aged child and IgE-mediated wheezing. Transient wheezing is associated with symptoms that are limited to the first 3-5 years of life, decreased lung function, maternal smoking during pregnancy and exposure to other siblings or children at daycare centers [37]. 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 [37]. 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 [38].

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.

A patient presented with paroxysmal dyspnea, 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 ≥ 20% and the forced expiratory volume in one second was increased by ≥ 12% and ≥ 200 mL in absolute volume by β2 agonist inhalation and a positive methacholine challenge test, respectively. In this case, the diagnosis of asthma can be readily established [39].
It is important to establish that the asthmatic has been provided with and indeed taken an appropriate dose of inhaled or oral corticosteroid therapy. Under-treatment is consistently recognized in fatal and near fatal asthma and is frequently the most important contributor to poor asthma control [40]. Patients with the highest levels of adherence to treatment have significantly fewer exacerbations than those with a confirmed record of poor compliance. Reported levels of compliance to treatment with inhaled corticosteroid therapy has ranged from as low as 30% in adolescents to 55% in adults [41], with similarly poor compliance with oral corticosteroids demonstrated in some studies.

Unfortunately, about 10% of asthmatics appear to have refractory disease despite receiving optimal therapy, leading to increased morbidity and increased costs associated with treatment[42]. In making the diagnosis of refractory asthma, it is important to consider and exclude other diseases in the differential diagnosis of wheeze, dyspnea, cough, and eosinophilia. Specifically, patients should be evaluated for other diseases such as chronic obstructive pulmonary disease, bronchiectasis (including allergic bronchopulmonary aspergillosis and cystic fibrosis), and vocal cord dysfunction [42].

Refractory asthma encompasses wide ranges in both clinical symptoms and in natural history. Patients may appear to have highly labile disease, with wide swings in peak flows, while others are more chronically and severely obstructed. Other patients produce copious amounts of phlegm, some have associated sinus disease and gastroesophageal reflux, while others do not [42]. In poorly controlled asthma, add on therapies used as part of combination treatment include bronchodilators, mainly long-acting β-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 [43].

Does Asthma Predispose Patients To Get GERD?

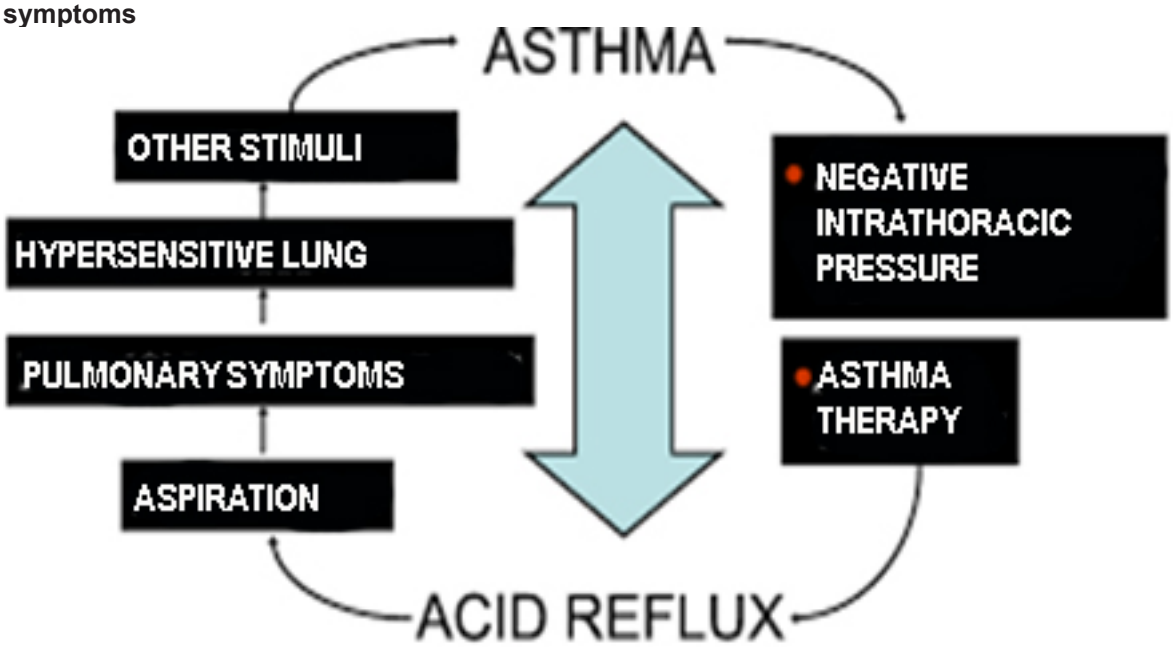
Pathophysiologically, asthma may predispose an individual to the reflux of gastroduodenal contents into the esophagus by a variety of mechanisms, including the following: increased intrathoracic pressure, vagus nerve dysfunction, altered diaphragmatic crural function, and decreased lower esophageal sphincter (LES) pressure due to medical therapies for asthma [44]. LES motility and esophageal pH were assessed in eight subjects with intermittent asthma and eight healthy volunteers during three consecutive 30-minute periods: baseline, methacholine-induced bronchospasm, and after inhalation of the beta2-agonist salbutamol. They concluded that in patients with asthma, methacholine-induced bronchospasm increases the rate of transient LES relaxation (TLESR) and the number of reflux episodes [44]. Airway obstruction may also predispose asthma patients to GERD by relaxing the lower esophageal sphincter (LES). Zerbib et al showed that airflow obstruction significantly increased the number of LES relaxations and the number of reflux episodes [44]. The number of LES relaxations decreased when airflow obstruction was reversed.

Negative pleural pressures can increase the pressure gradient between the thorax and abdominal cavity promoting reflux [45]. In a study that found that among the asthmatic group 22 patients (44%) had GER and the main mechanism for GER triggering asthma is the vagally mediated reflex initiated by acid in the distal esophagus [46].

Bronchodilator medications may also decrease LES pressure. The theophylline treatment caused a significant increase in total reflux time and reflux symptoms but did not worsen the asthma. Patients with sub-therapeutic serum levels showed significant improvement in lung function and those with therapeutic serum levels did not [47]. In a randomized, double-blind crossover study, Hubert et al [48] administered oral theophylline or placebo to asthmatics finding no difference in the number of reflux episodes or total acid exposure time while pulmonary function improved. In addition, Ekstrom and Tibbling [47] examined 25 asthmatics with GERD using 24-hour esophageal pH testing and found that asthmatics with therapeutic theophylline levels had a 24% increase in total esophageal acid exposure. It is concluded that theophylline, in view of its potential to exacerbate GO-reflux, should be used with caution as maintenance therapy in asthmatic patients with GO-reflux [47]. Inhaled albuterol reduced lower esophageal sphincter LES basal tone and contractile amplitudes in the smooth muscle esophageal body in a dose-dependent manner. Inhaled beta (2)-agonists may increase the likelihood of acid reflux in a subset of patients who receive cumulative dosing [49].

A study that measured the lower esophageal sphincter pressures and studied gastroesophageal reflux patterns over 24 hours using an ambulatory Gastroreflux Recorder (Del Mar Avionics, Irvine, CA) in 44 controls and 104 consecutive adult asthmatics, found that most adult asthmatics, regardless of the use of bronchodilator therapy, have abnormal gastroesophageal reflux manifested by increased reflux frequency, delayed acid clearance during the day and night, and diminished lower esophageal sphincter pressures [50]. On the other hand Field et al reported that no asthma medications were associated with an increased likelihood of having GERD symptoms[51]. However, in conclusion, these data suggest that asthma should be treated aggressively with bronchodilators and anti-inflammatory agents; however, theophylline should be used carefully in asthmatics with GERD.

Figure 2: Asthma and GERD may exacerbate each other. GERD may induce bronchospasm, and asthma may induce GERD. Breaking the cycle by aggressively treating both conditions is the key to mitigating patients' symptoms



Does GERD in infants increase asthma risk?

Gastroesophageal reflux (GER), the regurgitation of gastric contents into the esophagus or mouth, is a common phenomenon among healthy infants, with approximately 50% of 0- to 3-month-old infants and 67% of 4-month-old infants experiencing at least one episode of vomiting per day[52]. It is unknown whether gastroesophageal reflux disease (GERD) during infancy affects infant bronchiolitis severity or childhood asthma inception. Although bronchiolitis increases the risk of childhood asthma development, and childhood GERD and asthma are associated[53]. Cough was the most prevalent pulmonary symptom in infants with gastroesophageal reflux disease (GERD), according to findings presented at the CHEST Annual Meeting, held October 6-10, 2018 in San Antonio, Texas. Dr Silveyra and colleagues at NYU Winthrop Hospital in Mineola, New York, conducted a retrospective review of 262 patients with GERD (ages 0-12 months). A total of 138 (53%) patients had pulmonary symptoms and 124 (47%) did not have pulmonary symptoms. Cough was the most prevalent symptom at 47% vs wheezing or breathing difficulty. He found that patients with pulmonary symptoms had a higher incidence of early onset asthma (63%; median age at diagnosis, 8.4 months) and use of albuterol (92%) than patients without pulmonary symptoms [54]. It is not known if pre-existing GERD modulates the severity of infant bronchiolitis or is associated with increased risk of childhood asthma diagnosis. In a study among 432 infants with acute respiratory illness, 45 (10.4%) had parentally reported GERD. Infants with reported GERD were more likely to be white, have a parent with allergic rhinitis, and have a history of previous treatment for wheezing. Infants with reported GERD had a slightly lower median gestational age compared with infants without reported GERD [55]. Robert S. Valet studied four hundred thirty-two infants presenting with acute respiratory illness due to bronchiolitis or upper respiratory infection. Those studied with primary exposure had a parental report of a previous GERD diagnosis. He found that GERD during infancy may contribute to acute respiratory illness severity, but is not associated with asthma diagnosis at age 4 years[56].

Chronic cough and GERD

Chronic cough is a troublesome disorder in many ways. Cough is the most common reason why people seek medical help. Gastro-esophageal reflux (GER), in addition to asthma and postnasal drip syndrome (PNDS), is considered a common cause of chronic cough in all age groups. Chronic cough (> 4 weeks duration) [57] in children, a common presenting symptom to pulmonologists and allergists, is associated with burden (e.g. recurrent doctor visits and use of medications) and impaired quality of life to the child and their parents [58].

Whether gastroesophageal reflux (GER) or GER disease (GERD) causes chronic cough in children is controversial. GERD is commonly reported to be associated with chronic cough in adults [59]. It has not been commonly identified as the cause of pediatric cough [60]. It should be noted that many patients with chronic cough possibly due to gastro-oesophageal reflux disease do not have the typical symptoms associated with gastro-oesophageal reflux disease (i.e., heartburn and regurgitation) [61].

There are two proposed mechanisms of GERD associated cough: (1) acid in the distal esophagus stimulating an esophageal-tracheobronchial cough reflex, and (2) micro-aspiration or macro-aspiration of esophageal contents into the larynx and tracheobronchial tree. Irwin et al,[62] using dual-probe 24-hour esophageal pH testing with

the distal pH electrode placed at least 6 cm above the gastroesophageal junction and the proximal pH electrode in the proximal esophagus at least 2 cm above the thoracic inlet, noted that cough occurred simultaneously with acid in the distal esophagus 28% of the time vs 6% of the time in the proximal esophagus. In a study by Poe Robert [61] found that GERD was the single cause of cough in 24 patients (43%); twenty-nine patients (52%) had GERD plus another cause, and 3 patients (5%) had GERD with more than two causes; twenty-four patients (43%) had cough only, while 32 patients (57%) had other symptoms of GERD. When GERD causes cough, there may be no GI symptoms up to 75% of the time. While 24-hour esophageal pH monitoring is the most sensitive and specific test in linking GERD and cough in a cause-effect relationship [63]. On other hand some other studies concluded that acid may not be the sole mediator in gastric juice causing cough [64]. They also found that reflux occurred less often in the proximal than distal esophagus and that esophagitis was not necessary for coughing during acid infusions [64]. In conclusion, patients with chronic cough who also complain of typical and frequent GI complaints such as daily heartburn and regurgitation, especially when the findings of chest-imaging studies and/or clinical syndrome are consistent with an aspiration syndrome, the diagnostic evaluation should always include GERD as a possible cause [63].

Bronchopulmonary symptoms in GERD

In recent decades, GERD has become increasingly recognized as a potential cause of bronchopulmonary symptoms. While most studies have focused on asthma, many other pulmonary disorders have been linked to GERD, including aspiration pneumonia, interstitial pulmonary fibrosis, chronic bronchitis, and bronchiectasis. Pulmonary symptoms related to GERD include shortness of breath, wheezing, and chronic cough. Acid reflux should be considered if signs of GERD are present, symptoms are unexplained, or symptoms are refractory to therapy [65]. For many patients, pulmonary disorders may be the only indication that GERD is present.

Clinical presentations

Many patients with asthma report GERD symptoms (Table 1)[66], including heartburn, regurgitation, and dysphagia. Furthermore, respiratory symptoms related to reflux symptoms have been reported, as has the need for anti-reflux medication [67]. Additional to asthma, is vocal cord dysfunction syndrome. Vocal cord dysfunction syndrome has been associated with GER [68]. Paroxysmal laryngospasm, occurs with GER, with or without asthma, and may be confused with asthma. Nocturnal asthma symptoms are frequently present in patients with difficult-to-control asthma, raising the suggestion that GER contributes to both nocturnal symptoms and poor asthma control. Kiljander and colleagues reported that in patients with asthma with combined symptoms of GER and nocturnal asthma, treatment with esomeprazole resulted in a modest improvement in morning and evening peak flow [69].

Alternatively, some patients may have clinically silent GERD, especially in the context of difficult-to-treat asthma. A high degree of esophageal dysfunction has also been reported among patients with asthma, including esophageal dysmotility, LES hypotension, and a positive Bernstein test [70]. Specific esophageal motility abnormalities in asthma patients include ineffective esophageal motility, with a reported prevalence of 53.3%; nutcracker esophagus, with a prevalence of 7.6%; and low LES pressure, with a prevalence of 15.4% [71]. Endoscopy might also reveal esophagitis or Barrett's esophagus among patients with asthma, although most will not have esophagitis [72]. Compared with normal controls, patients with asthma have a higher frequency of reflux symptoms, more frequent LES hypotension by manometry, and increased esophageal acid contact times by 24-hour pH monitoring, which further supports the association between GERD and asthma [73].

Diagnosing GERD in Patients with asthma

All asthmatics should be carefully questioned about esophageal and extra-esophageal manifestations of GERD. Specific questions should include whether asthma symptoms occur after eating a large or a high-fat-containing meal, or with foods that are known to decrease LES pressure. It is also worthwhile to inquire if cough, dyspnea, or wheezing is associated with a reflux episode. Questions should also include whether frequent cough and hoarseness are present and whether asthma symptoms occur when lying down. In addition, inhaler use when experiencing GERD symptoms should be assessed [74]. Field et al [75] published an asthma and GERD questionnaire that can be incorporated into patient care. If the history is consistent with GERD and 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 [76], so no further diagnostic workup is necessary. Empiric therapy is considered successful if asthma outcomes are improved. Further testing is recommended in patients in whom empiric therapy is unsuccessful or who have symptoms suggesting complicated GERD (esophagitis, esophageal stricture, Barrett's esophagus, or neoplasm) [74]. Of note, many asthma patients with GERD do not experience reflux symptoms; this subset of patients may be difficult to diagnose. Ultrasonography is not indicated for GERD diagnosis as the results are clearly investigator-dependent. The sensitivity of ultrasound in the 15 minutes postprandial is about 95% but the specificity is only 11% in comparison to pH-metry [77].

Regarding scintigraphy, sensitivity and specificity are only moderate, at 69% and 78%, respectively [78]. Besides demonstrating tracer that refluxes into the esophagus, scintigraphy evaluates gastric emptying and may also show pulmonary aspiration.

Table 1: extraesophageal symptoms of GERD [66]

Extraesophageal manifestations of GERD

Pulmonary presentations	Otolaryngologic presentations
Asthma	Hoarseness
Aspiration pneumonia	Chronic cough
Interstitial pulmonary fibrosis	Throat clearing
Chronic bronchitis	Chronic laryngitis
Bronchiectasis	Globus sensation
Neonatal bronchopulmonary dysplasia	Vocal cord ulcers and granulomas
Sudden infant death syndrome	Laryngeal and tracheal stenosis
	Laryngeal cancer
	Mouth soreness
	Halitosis
	Pharyngitis
	Otalgia
	Chronic sinusitis
	Croup
	Stridor
	Dysphonia
	Abnormal taste
	Dental erosions

Prolonged 24-hour esophageal pH testing plays a key role in diagnosing GERD, especially in asthmatics without classic reflux symptoms, or those who are difficult to treat. In a study In children 6 to 17 years old with mild or moderate persistent asthma on inhaled corticosteroids, without GER symptoms, abnormal pH probe diagnostic of GER disease is present in 43%[79].

The American Gastroenterological Association's medical position statement on the clinical use of esophageal pH recording recommends testing asthmatics suspected of having reflux-triggered asthma [80].

Clinical clues and tests used in the diagnosis of GERD-associated asthma (81]

Clinical clues

1. Adult onset of asthma
2. No family history of asthma
3. Reflux symptoms preceding asthma onset
4. Wheezing worsened by meals, exercise, or supine position
5. Nocturnal cough or wheezing
6. Asthma worsened by theophylline or beta2-agonists
7. Asthma requiring prolonged systemic steroid therapy

Esophageal pH monitoring
Best test for GERD-related asthma; > 50% of adults with asthma have abnormal acid reflux. Most episodes of wheezing do not occur during reflux episodes, suggesting that multiple factors are involved

Barium studies
Helpful if they show hiatal hernia or reflux into proximal esophagus
Considerable variation in prevalence of esophagitis

Overnight gastroesophageal scintigraphy
More helpful in children than in adults

Uptake in chest (from stomach) suggests micro aspiration

The effect of GERD treatment on asthma patients

The 2007 National Asthma Education and Prevention Program Guidelines for the diagnosis and management of asthma recommend that clinicians consider treatment of reflux to improve asthma control in patients with poorly controlled asthma [83]. Data from adults with GERD and asthma have shown a wide variety of outcomes, ranging from no improvement to significant improvement in clinical status and pulmonary functions [84].

The current asthma guidelines recommend that medical management of GERD be instituted for patients who have asthma and complain of frequent heartburn (pyrosis), particularly those who have frequent episodes of nocturnal asthma [85]. Three categories of medications are widely available for the treatment of reflux disease: proton pump inhibitors (PPIs), H2 antagonists, and antacids.

Proton Pump Inhibitors: The PPIs are the most potent inhibitors of gastric secretion available and the recommended therapy when treating GERD-induced asthma. PPIs should be administered 30 to 60 minutes before meals. In randomised controlled trials of treatment for oesophageal reflux in children with a diagnosis of both asthma and gastro-oesophageal reflux, Meier et al[86] studied 15 asthma patients with GER in a double-blind placebo-controlled cross-over trial with omeprazole 20 mg twice daily for 6 weeks, with use of a more than 20% change in FEV1. 4 of 14 patients (29%) had omeprazole-responsive asthma, on evaluation of the 11 non-responders, 6 (45%) had esophagitis, and the non-responders had 3 to 5 times more esophageal acid than did the responders. This points out the importance of prolonged acid suppression before determining outcome, especially in patients with significant esophageal acid exposure [86]. Furthermore, Stordal et al [87] did not find any difference in asthma outcome or pulmonary function in children with GERD and undifferentiated asthma after 3 months of treatment with omeprazole. It is likely that a brief 3-month treatment may not be optimal for observing a difference, especially when both atopic and non-atopic children are included. Moreover, Størdal et al [87] also stated that acid suppression could relieve the asthma symptoms of patients with the more severe forms of asthma and GERD.

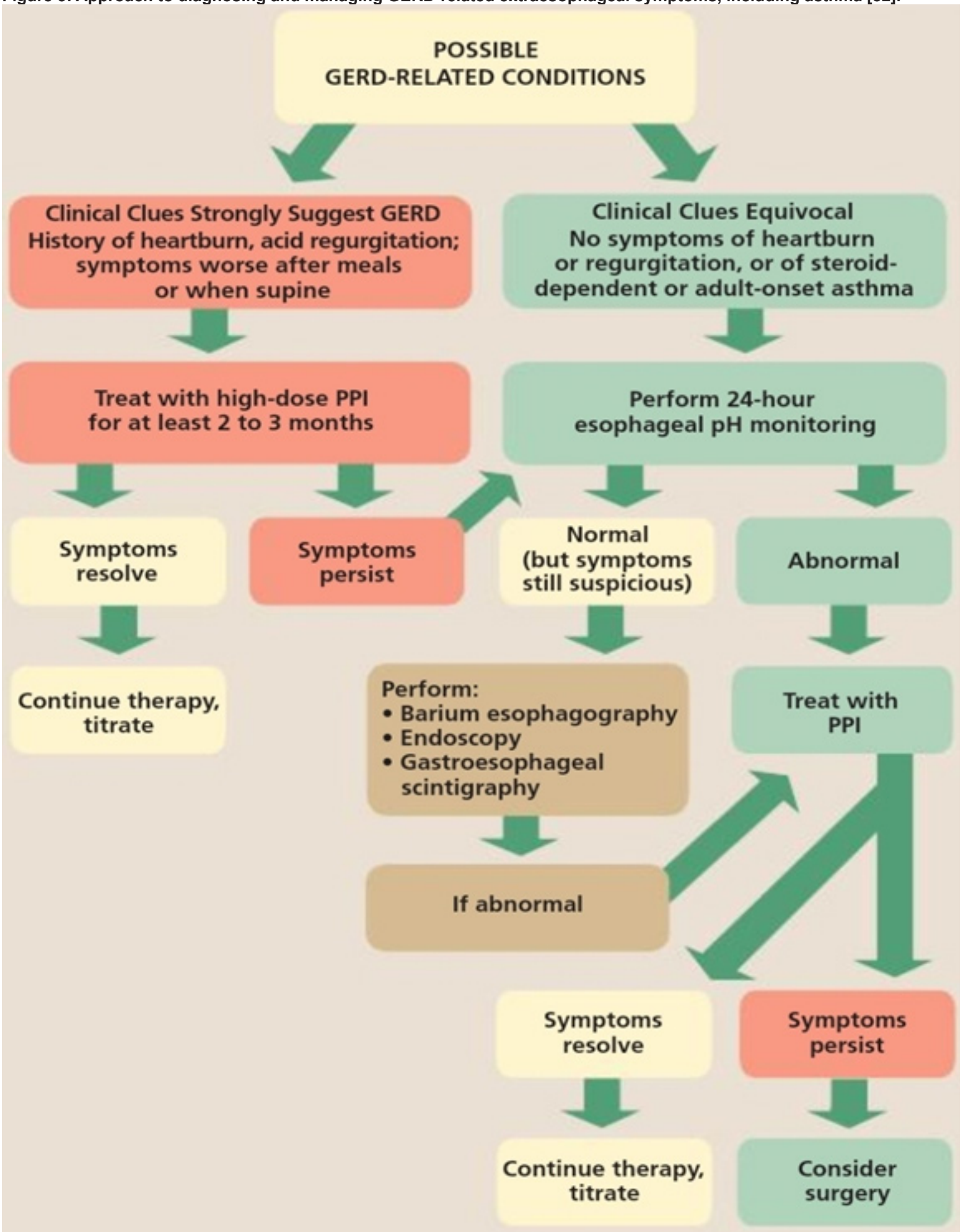
Yuksel et al [88] reported improvement in asthma symptoms in non-atopic children with GERD and asthma. Maev et al. 2003, showed that therapy of bronchial asthma associated with GERD using omeprazole in the dose equal to 40 mg per day or esomeprazole in the dose equal to 40 mg per day contributed to a reliable improvement of both pulmonary and esophageal symptoms. However, application of esomeprazole resulted in a faster reduction of bronchial obstruction and gastroesophageal reflux [89]. Although Levin et al. 1998, found improvement of peak expiratory flow rate and quality of life in asthmatics with gastroesophageal reflux after daily use of omeprazole 20 mg for 8 wk, the increase in FEV1 failed to reach statistical significance [90].

The guidelines drawn up by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) for asthma management [91] examine this topic. They report that the systematic review by Coughlan et al [92] selected 12 double-blind, randomized clinical trials with adults, and reported that GERD treatment did not improve asthma symptoms or lung function in concomitant asthma and GERD. A reduction in dry cough was reported, although this was probably not caused by asthma. The BTS-SIGN guidelines [91] conclude that any GERD must be treated, even if this generally has no impact on asthma. GERD may simply represent just an associated unrelated finding with asthma; it may worsen the severity of asthma, or could be a consequence of asthma itself [93].

Antacids: Antacids relieve heartburn and dyspepsia by neutralizing gastric acid. In addition to increasing the intragastric pH, they may also increase LES pressure. Generally, antacids have a short duration of action, requiring frequent daily administration.

Lifestyle Modifications: Asthma symptoms associated with GERD can be aggravated by high-fat meals that delay gastric emptying and foods that lower LES pressure. Eating or drinking acidic foods may also trigger symptoms[94].

Figure 3: Approach to diagnosing and managing GERD-related extraesophageal symptoms, including asthma [82].



Conclusion

The diagnosis and management of GER in asthmatic patients have remained challenges for years. Health care providers should be aware that GERD is a potential trigger of asthma, although not all asthma patients with GERD experience reflux symptoms. All patients with asthma should be questioned about reflux symptoms. If GER symptoms are present, then a 3-month therapeutic trial with high-dose proton pump inhibitors should be considered to see whether asthma improves. Further work is needed to evaluate the most cost-effective approach to providing therapy to these patients. Nevertheless, all patients with chronic cough or asthma should be aggressively investigated for the possibility of GERD propagating their disease.

Abbreviations: GERD= gastroesophageal reflux disease; LES=lower esophageal sphincter; PEF=peak expiratory flow, PPI: proton pump inhibitor, TENOR: The Epidemiology and Natural History of Asthma Outcomes and Treatment Regimens

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