

Gastroesophageal reflux: a potential asthma trigger

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Gastroesophageal reflux (GER), the retrograde movement of gastric contents into the esophagus, afflicts millions of Americans. A population-based survey of randomly selected adults shows that the prevalence rate of heartburn or regurgitation at least weekly approaches 20% [1]. Sir William Osler formally recognized GER as a potential trigger of asthma and stated "...attacks may be due to direct irritation of the bronchial mucosa or indirectly, too, by reflex influences from stomach..." [2]. Since Osler's time, we have gained significant insight into the association between asthma and GER [3].

Gastroesophageal reflux prevalence and epidemiologic considerations in asthmatics

GER symptoms are common in adults and children with asthma. Field et al [4] examined 109 asthmatics and 135 subjects in two control groups and found that heartburn was present in 77% of asthmatics compared with 50% of subjects in the control groups. Furthermore, 41% of asthmatics noted GER-associated respiratory symptoms, and 28% used their inhalers while experiencing GER symptoms. These data verify that GER symptoms are more prevalent in asthmatics compared

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with control populations and that asthmatics associate GER symptoms with their asthma symptoms. This high prevalence was verified by Perrin-Fayolle et al [5], who found that 65% of consecutive asthmatics had GER symptoms. Asthma symptoms also correlated with esophageal acid events on 24-hour esophageal pH testing. Our laboratory noted that of 151 respiratory symptoms reported during 24-hour esophageal pH testing, 119 (79%) were associated with esophageal acid [6]. Approximately 50% of children with asthma have GER symptoms [7].

GER may be clinically “silent” in asthmatics. In difficult-to-control asthmatics who did not have GER symptoms, Irwin et al [8] found that 24% had GER-responsive asthma. Our laboratory observed in consecutive asthmatics without GER symptoms that 62% of them had abnormal esophageal pH tests [9]. Demographic variables did not identify asthmatics with clinically silent GER. In children, GER was detected by scintigraphy in 23% of asthmatics who did not have GER symptoms [10].

Biopsy-proven esophagitis was found in 43% of consecutive adult asthmatics [11]. In children, esophagitis was present in 8.5% of asthmatics who had abnormal esophageal pH tests [12]. Sontag et al [13] performed esophageal pH tests in consecutive asthmatics and reported abnormal esophageal acid contact times in 82%. Compared with control subjects, asthmatics had more frequent reflux episodes and higher esophageal acid contact times. Our laboratory showed that 72% of asthmatics with GER symptoms had abnormal esophageal acid contact times [6]. Abnormal esophageal acid contact times are prevalent in children. Cinquetti et al [12] examined 77 asthmatic children age 39 to 170 months and reported abnormal esophageal acid contact times in 47 (61%). Asthma severity was proportional to esophageal acid amounts, and nocturnal GER was more frequently found in the moderate and severe asthmatics compared with the mild asthmatics [12]. Tucci et al [14] noted that 75% of asthmatic children had abnormal esophageal acid contact times.

Although many of the above studies used selected populations, asthmatics, compared with control subjects, have a higher frequency of GER symptoms and higher esophageal acid contact times. In general, approximately 50% to 80% of adults and children with asthma have GER (Table 1).

Table 1
Prevalence of gastroesophageal reflux in asthmatics

Findings	Prevalence	
	Adults	Children
Heartburn	77%	50%
Reflux-associated respiratory symptoms	41%	—
Clinically silent GER	62%	23%
Esophagitis	43%	5.85% ^a
Abnormal esophageal pH	82%	75%

^a Children with abnormal esophageal pH tests.

Epidemiologic considerations also give insight as to how GER may affect asthma. A case-control study examined more than 101,000 veterans discharged with esophagitis or esophageal stricture from 172 Veterans Administration hospitals and compared them with randomly selected veterans without esophageal disease. The veterans with significant esophageal disease had a 1.51 odds ratio (OR) of having asthma [15]. Gislason et al [16] examined the association between respiratory symptoms and nocturnal GER in a population-based study of more than 2600 young adults from three European countries. Subjects with nocturnal GER, compared with those without nocturnal GER, had a higher likelihood of wheezing (adjusted OR 2.5, 95% confidence interval [CI] 1.6–3.9) and physician-diagnosed asthma (adjusted OR 2.2, 95% CI 1.0–4.7). Asthmatics with nocturnal GER had greater peak expiratory flow rate (PEF) variability. These data support the hypothesis that GER during sleep has the potential to alter pulmonary function during the night. In a large prospective cohort study of more than 6500 asthmatics, Diette et al [17] noted that asthmatics over 65 years of age had higher heartburn prevalence compared with younger asthmatics and that GER was a risk factor for asthma hospitalizations. That GER was a risk factor for asthma hospitalization was verified by Shireman et al [18], who performed a retrospective cross-sectional analysis of Ohio Medicaid claims over 12 months involving 11,000 asthmatics. GER was predictive for a higher number of oral corticosteroid bursts ($P < 0.001$) and for an increased risk of asthma-related hospitalizations ($P < 0.007$).

There also are epidemiologic studies examining children. El-Serag [19] performed a case-control study in 10,000 children without neurologic defects (1980 subjects with GER and 7920 control subjects without GER) and reported that children with GER had a higher asthma prevalence compared with control subjects (13% versus 7%, $P < 0.001$). Even after adjusting for differences in age, gender, and ethnicity, GER remained a significant risk factor for asthma, with an OR of 1.9 (95% CI 1.6–2.3, $P < 0.001$). All of these studies show that GER prevalence is high in children and adults with asthma and that the two diseases may interact.

Predisposing factors to gastroesophageal reflux development in asthmatics

Under normal conditions in the stomach, the angle of His acts as a flap valve to prevent material from leaving the stomach. The lower esophageal sphincter (LES) is the major anti-reflux barrier and has an intrinsic basal tone along with augmentation by crural diaphragm contractions [20]. If GER occurs, a swallow initiates peristalsis that clears gastric contents from the esophagus. Saliva neutralizes the acid pH and rinses the refluxate from the esophageal mucosa. GER disease is a multifactorial process resulting from three potential motility abnormalities, including an incompetent LES, inefficient esophageal clearance of refluxed material, and delayed gastric emptying. Transient LES relaxations are LES relaxations not associated with swallows and are responsible for

approximately 75% of GER episodes in adults [20]. Specific predisposing factors for GER development in asthmatics include an increased pressure gradient between the thorax and the abdominal cavity (over-riding the LES pressure), autonomic dysregulation, and the high prevalence of hiatal hernia and obesity found in asthmatics. Asthma medications may promote GER [3].

Asthmatics can have an increased pressure gradient between the thorax and the abdominal cavity. At the end of expiration, the pressure gradient between the stomach and esophagus is 4 to 5 mm Hg [20]. Therefore, a normal LES pressure of 10 to 35 mm Hg is sufficient to counteract this pressure gradient. However, with airflow obstruction, especially during asthma exacerbations, a more negative pleural pressure is produced that may overcome the LES pressure, thus promoting GER.

Autonomic dysregulation may potentiate GER because transient LES relaxations are vagally triggered [20,21]. Our laboratory showed that asthmatics with GER have heightened vagal responsiveness [22]. Heightened vagal tone can result in a decreased LES pressure and stimulate transient LES relaxations [20,21].

Another factor is alteration in crural diaphragm function. The crural diaphragm contributes to LES pressure generation, especially during inspiration [20]. Hyperinflation associated with bronchospasm places the crural diaphragm at a functional disadvantage because of geometric flattening [23].

Hiatal hernias also predispose to GER and are common in asthmatics. Mays et al [24] noted that 64% of asthmatics, compared with 19% of control subjects, had hiatal hernia. Sontag et al [11] performed endoscopies in 186 consecutive asthmatics and reported the presence of hiatal hernia in 58%. Obesity contributes to GER, and GER is associated with an increased body mass index (BMI) and asthma symptoms as noted in the European Community Respiratory Health Survey [16,25].

Finally, medications including theophylline, albuterol, and oral corticosteroids may predispose to GER development. Theophylline increases gastric acid secretion and lowers LES pressure [26]. Ekström et al [27], in a placebo-controlled trial, noted that GER symptoms increased 170% and daytime reflux increased 24% with theophylline. However, there are conflicting data about the importance of theophylline [28]. Crowell et al [29] performed a prospective randomized double blind, placebo-controlled, crossover trial evaluating the effects of sequential doses of nebulized albuterol (2.5–10 mg) on esophageal manometry. Nebulized albuterol produced a dose-dependent reduction in LES pressure from 17 to 8.9 mm Hg. Furthermore, the amplitude of esophageal contractions at 5 cm and 10 cm above the LES was compromised [29]. Our laboratory examined the effect of oral corticosteroids on esophageal acid contact times in a prospective, placebo-controlled, crossover trial in 20 stable, moderate-persistent asthmatics. Oral prednisone, 60 mg per day for 7 days, resulted in significant increases in esophageal acid contact times at the proximal and distal esophageal pH probes [30]. These factors may contribute to the increased GER prevalence in asthmatics.

Potential mechanisms of gastroesophageal reflux–triggered asthma

There are many mechanisms whereby the esophagus and lung can interact and result in esophageal acid–induced bronchoconstriction. Neurogenic inflammation plays a role in many of these mechanisms. Mechanisms include a vagally mediated reflex (whereby acid in the esophagus triggers airway responses), a direct axonal reflex (whereby the central nervous system [CNS] is not required to complete a reflex arc), heightened bronchial reactivity, and microaspiration [26]. Esophageal acid also causes increases in minute ventilation without altering pulmonary function [31].

Vagal reflex

The tracheobronchial tree and the esophagus share common embryonic foregut origins and autonomic innervation through the vagus nerve. In a dog model, Mansfield et al [32] noted that esophageal acid causes an increase in respiratory resistance that was abolished with vagotomy. We reproduced this finding in a human model noting that esophageal acid reduces PEF rates and increases specific airway resistance without evidence of microaspiration [33]. Wright et al [34] measured spirometry before and after esophageal acid infusions and reported that esophageal acid caused decreases in heart rate, FEV₁, and oxygen saturation, which did not occur with atropine pretreatment. These data show that a vagal mechanism is active.

Local axonal reflex

Fischer et al [35] noted, with morphologic studies, that there is a direct neuronal connection between the esophagus and the lung via nitric oxide–containing neurons. In a guinea pig model, when nociceptive afferent nerves are stimulated in the esophagus without CNS intervention, there is the release of tachykinins in the lung, including substance P and neurokinin-A, as the result of a local axonal reflex [36].

Heightened bronchial reactivity

Vincent et al [37] showed a correlation between the amount of methacholine required to reduce the FEV₁ by 20% and the number GER episodes on esophageal pH testing ($R = 0.56$, $P = 0.05$). This relationship was even stronger in asthmatics with documented GER by esophageal pH tests ($R = 0.98$, $P = 0.001$). Heightened bronchial reactivity with GER was noted during sleep by Cuttitta et al [38], who monitored esophageal pH and respiratory resistance in seven asthmatics with GER. Esophageal acid was associated with an increase in lower respiratory resistance. There was also a correlation between GER episode duration and increase in lower airway resistance. These studies illustrate that esophageal acid primes the respiratory system so that when asthmatics

are exposed to another asthma trigger, such as cat dander, they have a heightened response.

Microaspiration

Microaspiration causes significant airway responses in animal models and in humans. In a cat model, Tuchman et al [39] noted that 50 μ L of tracheal acid caused a 5-fold increase in total lung resistance compared with a 1.5-fold increase with 10 mL of esophageal acid. The vagus nerve also plays a role in the microaspiration model because vagotomy ablated the tracheal acidification response. In humans, Jack et al [40] monitored tracheal and esophageal pH and reported that GER episodes associated with tracheal and esophageal acidification decreased PEF rates by 84 L/min compared with 8 L/min when esophageal acid alone was present.

Neurogenic inflammation

All of these mechanisms can result in neurogenic inflammation. In a guinea pig model, Hamamoto et al [41] noted that esophageal acid resulted in airway edema and the release of substance P. This airway edema was inhibited by a substance P receptor antagonist. Vagal and local axonal reflexes were responsible for these alterations. An acidic environment in the upper airway may also alter the inflammatory milieu [42]. Airway protective mechanisms may not be able to neutralize the acid load to the airway epithelium, thus exposing it to injury [43]. Esophageal contents may damage the airway epithelium, resulting in the release of cytokines and adhesion molecules, leading to neurogenic inflammation and the initiation of other inflammatory pathways [44].

Increased minute ventilation

Field et al [31] examined airway responses and respiratory mechanics in nonasthmatics during esophageal acid infusions. Minute ventilation increased with esophageal acid and decreased with esophageal acid clearance. Other respiratory parameters, including pulmonary function, did not change.

Asthma outcomes with anti-reflux therapy

Medical therapy

If GER is a potential asthma trigger, then aggressive GER therapy should improve asthma outcomes. Multiple studies have evaluated asthma outcomes, and most show an improvement in asthma symptoms. In reviewing the combined results of 12 studies examining medical therapy in 326 treated asthmatics with GER, asthma symptoms improved in 69%, medication use was reduced in 62%,

and evening PEF rates improved in 26% of patients; however, pulmonary function did not improve [45]. Most trials used H₂ receptor antagonists (H₂RAs) and not proton pump inhibitors (PPIs) [45]. More recently, the Cochrane Airways Group registry examined controlled trials, and 12 trials met their inclusion criteria. Although they noted no overall improvement in asthma after GER therapy, subgroups of patients may benefit. They point out the importance of examining predictors of asthma response [46]. Coughlan et al performed a power analysis on available data, noting that a study sample size of 506 subjects would be needed to detect a 20 L/min improvement in PEF [47].

We performed a prospective pretest/post-test evaluation of 30 asthmatics with GER using a 3-month trial of acid suppressive therapy using omeprazole (20–60 mg/d). Seventy-three percent of asthmatics with GER had at least a 20% increase in PEF rate and/or a 20% decrease in asthma symptoms. The asthma responders had improvement in pulmonary function including FEV₁ and PEF rates. Asthma symptoms required significant time to improve. After 1 month of acid suppressive therapy there was a 30% reduction in asthma symptoms compared with baseline, and by 3 months there was a 57% reduction. Twelve weeks of acid suppressive therapy was required for asthma symptom improvement. Approximately 30% of asthmatics did not have adequate acid suppression, documented by esophageal pH testing, on 20 mg/d of omeprazole [48].

More recently, eight placebo-controlled trials in adults using PPIs have been reported (Table 2). There are no reported double blind, placebo-controlled trials using PPIs in children. All of the studies contained small subject numbers and had inadequate power to address asthma outcomes as noted by the Cochrane Airways Group [47]. Five of the eight PPI trials defined asthma by using clinical and objective data, including airway reactivity (bronchodilatory response or

Table 2
Adult-controlled^a PPI trials in asthmatics with gastroesophageal reflux

Author	n	Crossover		Treatment	Asthma outcome
		design			
Ford et al [50]	10	Yes		Omp 20 mg × 4 wk	No change
Meier et al [80]	15	Yes		Omp 40 mg × 6 wk	29% ↑ FEV ₁ by 20% if esophagitis healed
Teichtahl et al [81]	20	Yes		Omp 40 mg × 4 wk	Mild improvement in PM PEF
Levin et al [82]	9	Yes		Omp 20 mg × 8 wk	Improved symptoms, PEF, and QOL
Boeree et al [49]	36	No		Omp 40 mg BID × 12 wk	Includes COPD, improved PM symptoms
Kiljander et al [83]	52	Yes		Omp 40 mg × 8 wk	Improved PM symptoms
Harmanci et al [84]	5	Yes		Omp 40 mg × 4 wk	Improved PM symptoms
Jiang et al [85]	30	No		Omp 20 mg + domperidone 10 mg TID × 6 wk	Improved FEV ₁ , PEF

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume at 1 s; Omp, omeprazole; PEF, peak expiratory flow; PPI, proton pump inhibitor; QOL, quality of life.

^a No pediatric-controlled PPI trials reported to date.

methacholine challenge tests). Six of the eight PPI trials were crossover in design, so that order and carryover effects could have interfered with results. Also, the duration of PPI therapy may have been too brief to show a treatment response. Only the Boeree et al [49] trial was of adequate duration (≥ 12 wk). Most trials did not document adequate acid suppression on therapy (eg, the Ford et al [50] trial used omeprazole 20 mg/d). Furthermore, asthma outcome variables were not consistently measured. Another potential limitation is that GER may not have been an asthma trigger for the individual subjects in the studies. A better study design may be a placebo-controlled parallel design with separate groups of treated and control subjects, using subjects who have GER as an asthma trigger. Not all asthmatics with GER have GER as a trigger of their asthma because asthma is heterogeneous concerning triggers and resultant bronchospasm.

A recently published abstract by Littner et al [51] reports asthma outcomes from the first multicentered, double blind, placebo-controlled trial using high-dose PPI therapy. Two hundred seven moderate to severe-persistent asthmatics with GER symptoms participated in this 24-week trial. Subjects were treated with lansoprazole 30 mg twice daily or placebo. Quality of life variables improved in the treatment group. Treated asthmatics had fewer asthma exacerbations and did not require prednisone bursts as often as the control asthmatics. This trial is the largest trial to date examining this topic.

Another potential way to examine asthma outcomes is to look at difficult-to-control or therapy-resistant asthmatics. Irwin et al [8] examined contributing factors in difficult-to-control asthmatics (those requiring 10 mg of prednisone at least every other day) by using a systematic management protocol. Treatment of GER and the addition of inhaled corticosteroids were the most helpful interventions. Heaney et al [52] examined predictors of therapy-resistant asthma using a systematic evaluation protocol and found that GER was prevalent in this population (57%). Khoshoo et al [53] examined the role of GER in children 5 to 10.5 years of age with persistent asthma and found that 59% had GER. Children with GER then had medical or surgical anti-reflux therapy [53]. All children with abnormal esophageal pH tests had a significant reduction in their asthma medications over the 1-year study period. Anti-reflux therapy resulted in the reduction of the use of short- and long-acting bronchodilators and inhaled corticosteroids. Another important finding from this study is that at least 6 months of anti-reflux therapy was required to see an appreciable response in asthma outcome in these children [53].

Surgical therapy

Surgical trials have also examined asthmatics with GER. Most trials were case series and had many design flaws, including the lack of a control group, poor documentation of adequate GER control postoperatively, and poor documentation of asthma outcomes. Field et al [54] examined asthma outcomes with anti-reflux surgery and identified 24 trials with 417 asthmatics. Anti-reflux surgery

Table 3

Surgical therapy in asthmatics with gastroesophageal reflux (all case series)

Author	<i>n</i>	Duration	Asthma outcome
Kennedy et al [86]	15	Unknown	100% improved
Overholt et al [87]	28	76 months	82% improved
Urschel et al [88]	27	Unknown	89% improved
Lomasney et al [89]	129	Unknown	75% improved
Sontag et al [90]	13	> 1 y	55% improved
Tardif et al [91]	10	1.75 y	50% improved
Perrin-Fayolle et al [61]	44	> 5 y	84% improved
DeMeester et al [92]	17	> 3 y	82% improved
Johnson et al [93]	14	3 y	Group improved
So et al [94]	16	> 1 y	48% improved
Patti et al [95]	39	2.3 y (median)	64% improved
Spivak et al [96]	39	2.7 y (median)	Group improved

improved GER variables in 90%, asthma symptoms in 79%, and asthma medication use in 80% of subjects. Pulmonary function improvement occurred in 27% of surgically treated asthmatics. Table 3 reviews the surgical outcome trials.

Randomized trials of medical versus surgical therapy

Two groups compared medical versus surgical therapy in GER-related asthma; however, PPIs were not used. Larrain et al [55] examined the effect of cimetidine 300 mg four times a day versus surgery in nonallergic asthmatics. After 6 months, there were improvements in pulmonary function, including FEV₁ and PEF, in both treatment groups but not in the placebo group. Medication use improved in both treatment groups. Asthma was improved in 74% of medically treated subjects and in 77% of surgically treated subjects, compared with 36% of control subjects. Sontag et al [56] performed a placebo-controlled randomized study comparing ranitidine 150 mg, three times a day, with surgery in 73 subjects. In the surgery group, 75% had improvement in asthma symptoms, compared with 9% of the medically treated group and 4% of the control group at 5-year follow-up. More recently, Sontag et al [57] examined 62 patients randomized to ranitidine, surgery, or placebo. At the end of 2 years, mean asthma symptom scores in the surgically treated group improved 43%, compared with < 10% in the medically treated and control groups. Some patients had up to 19 years of clinical follow-up after randomization.

Potential predictors of gastroesophageal reflux-responsive asthma

Despite the numerous design flaws in many of the studies, some studies have identified potential predictors for asthma response either by the use of selected patient populations or by evaluation of predictive variables in the responders

Box 1. Potential predictors of asthma response**Asthma characteristics:**

- Difficult-to-control asthma [8]
- Nonallergic intrinsic asthma [55]
- Nocturnal asthma [61]
- Obesity (BMI > 29.7 kg/m²) [60]

GER characteristics:

- Reflux-associated respiratory symptoms [58]
- Regurgitation more than once weekly [48]
- Proximal acid on pH testing [48,59]
- Distal acid on pH testing [59,60]

(Box 1). These predictors need to be verified in independent patient populations. Irwin et al [8] noted that difficult-to-control asthma is a potential predictor, whereas Ekström et al [58] noted that a history of reflux-associated respiratory symptoms predicted asthma improvement. Our laboratory noted that the presence of regurgitation more than once a week or the presence of proximal reflux on pH esophageal testing predicted asthma response [48]. Schnatz et al [59] noted that more severe distal reflux predicted asthma response. Kiljander et al [60] noted that higher esophageal acid contact times and a higher BMI predicted asthma improvement. Larrain et al [55] noted that their nonallergic intrinsic asthmatics had asthma improvement with anti-reflux therapy. Perrin-Fayolle et al [61] noted that nocturnal asthma predicted asthma response. If validated, these predictors could help the clinician identify which asthmatics are most likely to respond to anti-reflux therapy.

Diagnosis and therapy of gastroesophageal reflux in asthmatics*Diagnosis*

Making the diagnosis of GER in asthmatics is similar to making the diagnosis in people without asthma. GER symptoms may be intermittent, or continuous and progressive. Classic esophageal symptoms include heartburn, regurgitation, retrosternal and epigastric pain, dysphagia, cervical discomfort (globus), and belching [62]. GER symptoms may be temporally associated with chest tightness, wheezing or other asthma symptoms, and inhaler use [4,6]. GER may cause arousals from sleep. It may also be clinically silent in up to 62% of asthmatics without GER symptoms [9]. Esophageal pH testing is required to identify these asthmatics [9]. Many diagnostic tests are available for GER (Table 4).

Table 4

Diagnostic tests for gastroesophageal reflux accuracy in adults

	Sensitivity (%)	Specificity (%)
Empiric PPI trial [63]	70–80	85
Esophageal pH [65]	77–100	85–100
Endoscopy [68]	60 at best	90–95
Barium esophagram [63]	40	Depends
Bernstein test [63]	32–100	40–100
⁹⁹ Tc-sulfur colloid [63]	14–90	Up to 90

Abbreviation: PPI, proton pump inhibitor.

An empiric trial of acid suppression using a PPI is a simple and potentially definitive method for diagnosing and assessing GER as a potential asthma trigger in selected asthmatics. Response to PPI therapy can also assure a cause-and-effect relationship between GER and specific symptoms [63]. GER symptoms usually respond to PPI therapy within 7 to 14 days [63]. A minimum 3-month empiric trial of PPI should be used to assess asthma symptom improvement [48]. Fass et al [64] found that a 7-day trial of omeprazole 40 mg in the morning and 20 mg in the evening had a sensitivity of 78% and a specificity of 86% for diagnosing GER as the cause of noncardiac chest pain. An empiric trial has advantages, such as its availability, with preliminary evidence showing that it may be cost effective as well.

Ambulatory 24-hour esophageal pH testing is the gold standard for diagnosing GER and has a sensitivity and specificity that approaches 90% [65]. This test entails placing a pH probe intra-nasally and positioning it 5 cm above the LES (distal). Often, multi-channel pH probes are used to monitor pH at the distal and more proximal regions, including the pharynx. An event marker can be activated when GER or pulmonary symptoms occur. A reflux event is defined as a drop in pH below 4.0. The total percentage of time that the pH is <4.0 is the most useful measurement, with 5.5% being the upper limit of normal. Esophageal pH testing can be used to assess whether there is adequate control of esophageal acid while the patient is on anti-reflux therapy. More recently, a wireless pH probe (Bravo pH Probe; Medtronic, Minneapolis, MN) has become available that overcomes the disadvantages of catheter-related pH probes [66]. The wireless probe is endoscopically placed approximately 6 cm above the Z line that separates the gastric mucosa from the esophageal mucosa. The capsule gathers pH data for approximately 2 days [66]. Another new experimental technique is multi-channel intraluminal esophageal impedance that can be combined with pH monitoring [67]. This device measures the electrical impedance of the esophagus in multiple sites up and down the catheter system so that the movement of gases, liquids, and solids can be quantitated. This technique, when combined with esophageal pH, is useful when assessing for acidic and nonacidic GER [67].

Upper endoscopy is useful for detecting esophageal mucosal injury, including esophagitis, strictures, webs, Barrett's esophagitis, and esophageal tumors [68].

Endoscopy has a poor sensitivity, which limits its usefulness as a diagnostic test for GER. The same is true for the barium esophagram, which has a sensitivity of approximately 40% [63]. Other tests, including radio-labeled ⁹⁹technetium-sulfur colloid scintiscanning and the Bernstein test, have low sensitivities and are not useful [63]. In conclusion, an empiric trial of acid suppression using a PPI and 24-hour esophageal pH testing seem to be the best methods for detecting GER in asthmatics.

In children, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition developed guidelines concerning esophageal pH testing [7]. Children should be questioned about typical GER symptoms, and esophageal pH testing is recommended if persistent asthma is present. As in adults, most children with GER-triggered asthma do not have esophagitis, so endoscopy has a low sensitivity [12]. Empiric PPI trials can be considered in children, although no validation studies have been reported [7].

Therapy

Lifestyle changes are the cornerstone of GER therapy [68]. Lifestyle changes include weight loss (if the patient is obese), avoiding large meals, and avoiding meals within 3 hours of bedtime. Patients should avoid acidic foods, including carbonated drinks. Caffeine, chocolate and peppermint (which decrease LES pressure), and fatty foods (which delay gastric emptying) should be avoided. Antacids can be used for acute relief of GER symptoms. Raising the head of the bed with blocks or a wedge can reduce nocturnal GER. Assess whether theophylline is required because it can worsen GER.

Medical therapy includes gastric acid secretion inhibitors such as H₂RAs and PPIs. Prokinetic agents improve esophageal motility, increase LES pressure, and can be combined with other GER medications. First introduced in the 1970s, H₂RAs are safe and well tolerated, and all agents have approximately the same efficacy. Commonly used agents include cimetidine up to 800 mg twice daily or 400 mg four times daily, ranitidine 150 mg twice daily, nizatidine 150 mg twice daily, and famotidine 20 mg twice daily. These agents provide complete relief of heartburn in approximately 60% of patients [68]. PPIs achieve superior gastric acid suppression and directly inhibit the acid-secreting parietal cells, so PPIs should be given approximately 30 minutes to 1 hour before meals [68]. PPIs have an excellent safety profile. Patients have been on long-term omeprazole therapy for more than 16 years [69]. Currently available PPIs include omeprazole (Prilosec) 20 mg and 40 mg up to twice daily, lansoprazole (Prevacid) 30 mg once or twice daily, pantoprazole (Protonix) 40 mg once or twice daily, rabeprazole (Aciphex) 20 mg daily, and esomeprazole (Nexium) 40 mg up to twice daily. There are minimal clinically relevant differences among the PPIs [70]. Rabeprazole has a slightly faster onset on action than other PPIs; omeprazole has the highest potential for drug interactions with warfarin, diazepam, phenytoin, and theophylline; and pantoprazole has the lowest potential for drug interactions. None of the PPIs requires dosing adjustments for hepatic or renal insufficiency [70].

The only prokinetic agent available in the United States is metoclopramide. The usual dosing of metoclopramide is 10 mg four times daily. Metoclopramide causes CNS side effects, including drowsiness, irritability, and extrapyramidal effects, in approximately 20% to 50% of patients.

Anti-reflux surgery options include open and laparoscopic procedures. Fundoplication results in GER symptom resolution in approximately 80% to 90% of patients. However, surgery rarely replaces the need for anti-reflux medications [71]. Spechler et al [72] performed a prospective randomized trial of medical and surgical therapy in 160 patients with complicated GER, having a median follow-up of 10 years. Sixty-two percent of surgically treated patients continued to use anti-reflux medications regularly. Surgery also has risks. For instance, laparoscopic fundoplication is associated with a 12% risk of dysphagia. Surgery for treatment of GER-triggered asthma should be reserved for asthmatics who have marked improvement in their asthma with medical anti-reflux therapy.

There are endoscopic methods to treat GER, including endoscopic gastroplasty and the Stretta procedure, which delivers radio frequency energy below the mucosa at the gastroesophageal junction [73]. These endoscopic methods do not have outcomes data in asthmatics with GER-triggered asthma and should be considered experimental in this population.

Therapy in children

Therapy in children older than 2 years of age is similar to that of adults [74]. Lifestyle measures should be implemented. Metoclopramide is widely used, but CNS effects are common, affecting up to 20% of children treated. H₂ receptor antagonists, including cimetidine, are FDA approved in doses of 20 to 40 mg/kg/d divided into four doses. Ranitidine, 4 to 6 mg/kg/d, can be divided into two or three doses. PPIs are also effective [75]. Although not FDA approved for use in children, omeprazole is effective; however, it has a wide range of dosing requirements for adequate acid suppression (ranging from 0.7–3.5 mg/kg/d) [76]. Lansoprazole is FDA approved for use in children at a dose of 15 or 30 mg/d, dependent on the child's weight [77]. Surgical fundoplication can be performed in children; however, careful evaluation of esophageal and pulmonary parameters should be performed before considering surgical therapy.

Potential management strategy of gastroesophageal reflux–triggered asthma

Because anti-reflux therapy has the potential to improve asthma outcome in selected patients, all asthmatics should be assessed for GER. If GER symptoms are present, then an empiric trial of acid suppressive therapy should be considered. A PPI should be used because of its superior effectiveness and should be given at high doses, twice daily, for at least 3 months. Asthma symptoms, PEF rates, and asthma medication use should be monitored before and during the empiric trial [78]. Also, an empiric trial should be considered in asth-

matics with moderate or severe persistent asthma, especially in those requiring oral corticosteroids, even in the absence of GER symptoms. If asthma outcomes are improved at the end of the 3-month empiric trial, then GER therapy should be continued. Maintenance GER therapy could begin with tapering the PPI dose to once daily. Surgery could be considered in selected patients, especially in those with normal esophageal motility. If asthma outcomes are not improved at the end of the 3-month empiric trial, then GER is most likely not a trigger of the individual's asthma if GER is adequately controlled.

O'Connor et al [79] designed a disease model to examine the cost-effectiveness of strategies for diagnosing GER-triggered asthma and reported that an empiric omeprazole trial for 3 months, followed by 24-hour esophageal pH testing in the nonresponders, was the most cost-effective way to include or exclude GER as a trigger in individual asthmatics. There are no published trials examining the cost-effectiveness of medical versus surgical therapy in asthmatics with GER-triggered asthma.

Summary

GER is a potential asthma trigger. Further research is needed to elucidate the role of esophageal acid in perpetuating airway inflammation and for validating potential predictors for asthma response with anti-reflux therapy.

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