

Gastroesophageal reflux and asthma: Insight into the association

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Gastroesophageal reflux (GER) is a potential trigger of asthma. GER symptoms are more prevalent in asthma patients compared with control populations, with a prevalence of approximately 75%. GER symptoms are associated with respiratory symptoms and inhaler use. GER may also occur without esophageal symptoms. Abnormal esophageal acid contact times are also more prevalent in patients with asthma compared with control populations, with a prevalence of 80%. Pathophysiologic mechanisms of esophageal acid-induced bronchoconstriction include a vagally mediated reflex, heightened bronchial reactivity, and microaspiration. Esophageal acid may increase minute ventilation without evidence of bronchoconstriction. Esophageal acid is associated with the release of substance P in the bronchial mucosa, resulting in airway edema. Medical antireflux therapy with proton pump inhibitors results in asthma symptom improvement in approximately 70% of patients, similar to surgical results. Predictors of asthma response include the presence of regurgitation, proximal acid reflux, esophagitis healing with therapy, reflux-associated respiratory symptoms, or nocturnal asthma. Management of GER in adult patients with asthma should include a 3-month trial of high-dose proton pump inhibitor while monitoring asthma outcome. GER should be considered as a potential asthma trigger in all patients. (*J Allergy Clin Immunol* 1999;104:251-9.)

Key words: *Asthma, gastroesophageal reflux, microaspiration*

Asthma is a disease in which multiple triggers ignite an inflammatory response producing airway edema, inflammatory mediator release, smooth muscle contraction, and increased mucous secretion. Gastroesophageal reflux (GER) is a potential trigger of asthma.¹ GER is a condition in which gastric contents flow in a retrograde direction across the gastroesophageal junction into the esophagus, causing symptoms or structural esophageal changes. Asthma and GER are both common in the

Abbreviations used

GER:	Gastroesophageal reflux
LES:	Lower esophageal sphincter
PD ₂₀ :	Provocative dose of methacholine required to produce a fall in FEV ₁
PEF:	Peak expiratory flow rate

human population and may coexist without a direct interaction.^{2,3}

To solidify the association between asthma and GER, 3 criteria should be considered. First, patients with asthma should have a higher prevalence of GER than individuals without asthma. Second, physiologic mechanisms between GER and asthma should explain how the 2 disease processes interact. Third, if GER exacerbates asthma, then antireflux therapy should improve asthma outcome. Because exacerbating factors of asthma are multiple, predictive variables should identify subsets of asthma patients who respond to antireflux therapy. This review will examine GER prevalence in patients with asthma, examine physiologic mechanisms of how GER and asthma may interact, examine asthma outcome with antireflux therapy, and review a management approach to GER in adult patients with asthma.

PREVALENCE OF GER IN PATIENTS WITH ASTHMA

The prevalence of GER among patients with asthma is estimated to be between 33% and 89%.⁴ In a survey of 150 consecutive asthma patients in France, 65% reported reflux symptoms.⁵ In a Veterans Administration population, heartburn was reported in 72% of 189 consecutive asthma patients, with 50% reporting supine nocturnal heartburn.⁶ More recently, Field et al⁷ examined 109 asthma patients and 135 subjects in 2 control groups. Heartburn was present in 77% of the asthma patients compared with 52% and 48% of patients in the 2 control groups ($P < .05$). The prevalence of regurgitation was 55% in the patients with asthma, with 24% reporting dysphagia. In the week before filling out the questionnaire, 45% of the asthma patients had heartburn, 22% had regurgitation, and 24% had dysphagia. Even more interesting is that in the week before completing the ques-

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tionnaire 41% of the asthma patients noted reflux-associated respiratory symptoms, and 28% used their inhalers while they were experiencing GER symptoms. This eloquent questionnaire-based, cross-sectional analysis study showed not only that asthma patients have a higher prevalence of GER symptoms compared with 2 control groups, but that they also associate GER symptoms with asthma symptoms.

Esophageal dysmotility, a physiologic mechanism for developing GER, is also prevalent in asthma patients. Kjellen et al⁸ found that 38% of 97 consecutive patients with asthma had esophageal dysmotility and 27% had lower esophageal sphincter (LES) hypotension. Sontag et al⁹ found that, compared with controls, 104 consecutive asthma patients had significantly lower LES pressures ($P = .001$). Also, in another report of 34 consecutive nonallergic patients with asthma undergoing esophageal manometry because of gastrointestinal symptoms, 23 (68%) had esophageal dysmotility.¹⁰ Asthma patients also have a high prevalence of esophagitis, with 43% of 186 consecutive patients having esophagitis.¹¹

Ambulatory 24-hour esophageal pH monitoring is the most reliable test for diagnosing GER, with a sensitivity and a specificity of >90%.¹² The prevalence of abnormal esophageal acid contact times is higher in patients with asthma compared with healthy control subjects. Sontag et al⁹ found that 85 of 104 (82%) consecutive asthma patients had abnormal esophageal acid contact times. Compared with healthy control subjects, patients with asthma had more frequent reflux episodes ($P < .001$) and had higher esophageal acid contact times ($P < .001$). In another selected group of 17 nonallergic asthma patients, 14 of 17 (82%) had abnormal esophageal acid contact times, especially while in the supine position.¹⁰ Another study of 105 consecutive asthma patients showed that abnormal esophageal acid contact times were present in 32%.¹³ More recently, Harding et al¹⁴ showed that, of 199 asthma patients referred for 24-hour esophageal pH testing, 72% with reflux symptoms had abnormal esophageal acid contact times. There was also a correlation between respiratory symptoms and esophageal acid events, with 78% of respiratory symptoms being associated with esophageal acid. Ninety percent of coughs were associated with esophageal acid events.

In addition, some asthma patients have significant GER without esophageal symptoms. Irwin et al¹⁵ found that in difficult-to-control asthma patients without reflux symptoms, 24% had GER-responsive asthma. Similarly, Harding et al¹⁴ noted that 24% of asthma patients without esophageal reflux symptoms had abnormal esophageal acid contact times. Twenty-four-hour esophageal pH testing is required to identify these "clinically silent" cases.

Finally, a case-controlled study involving 101,366 veterans discharged from 172 Veterans' Administration Hospitals with the diagnosis of esophagitis or esophageal stricture compared them with randomly selected veterans without the diagnosis of esophageal disease.¹⁶ The veterans with significant esophageal disease had a higher likelihood of having asthma than did veterans without esophageal disease, with an odds ratio of 1.51.

Although many studies included selected populations, asthma patients compared with control populations have a higher frequency of reflux symptoms, esophageal dysmotility, and higher esophageal acid contact times. A conservative estimate that at least 50% of asthma patients have GER is supported by multiple studies. Most studies show that approximately 80% of patients with asthma have GER.

FACTORS PROMOTING GER IN PATIENTS WITH ASTHMA

Factors that may promote GER in patients with asthma include autonomic dysregulation, an increased pressure gradient between the thorax (esophagus) and the abdominal cavity (stomach), crural diaphragm function, and use of bronchodilators.

Asthma patients have evidence of autonomic dysregulation.¹⁷ In 73 autonomic function tests performed in asthma patients with GER, a normal response was found in 20 (27%), a hypervagal response in 37 (51%), a hyperadrenergic response in 6 (8%), and a mixed response in 10 (14%). These data suggest that asthma patients with GER have heightened vagal responsiveness. Autonomic dysregulation could result in decreased LES pressure and transient relaxations of the LES, principal mechanisms of GER.¹⁸

The second factor predisposing to GER is an increased pressure gradient between the thorax (esophagus) and the abdominal cavity (stomach). At the end of expiration the pressure gradient between the stomach and the esophagus is 4 to 5 mm Hg.¹⁸ Thus a normal LES pressure of 10 to 35 mm Hg at end expiration is sufficient to counteract the pressure gradient; however, with airflow obstruction a more negative pleural pressure may increase the pressure gradient, thus promoting reflux.

A third factor that may promote GER is alteration in crural diaphragm function. The crural diaphragm contributes to LES pressure generation.¹⁸ Investigators have shown that transient relaxation of the LES and the crural diaphragm are responsible for GER.¹⁹ Hyperinflation associated with bronchospasm places the crural diaphragm at a functional disadvantage because of geometric flattening.²⁰

Finally, bronchodilator medications may alter GER. Ekström and Tibbling²¹ evaluated 25 patients with moderate-to-severe asthma who had a history of GER in a single-blind, placebo-controlled trial. Patients underwent 2 consecutive esophageal pH tests, 1 with and 1 without their ordinary doses of slow-release theophylline. Day-time reflux increased 24% during theophylline therapy. Symptoms of GER increased 170%, whereas respiratory symptoms and pulmonary function improved with theophylline.²¹ There are also conflicting results. Hubert et al²² performed a double-blind cross-over study in 16 patients with asthma and found no significant difference in 24-hour esophageal pH variables regardless of whether patients were receiving theophylline or placebo. Oral β_2 -adrenergic agonists may decrease LES pressure²³; however, inhaled β_2 -adrenergic agents caused no significant change in GER parameters or esophageal motility.²⁴

There are also studies evaluating the effect of multiple bronchodilators on esophageal pH parameters. Sontag et al¹¹ found no difference in esophagitis prevalence regardless of whether asthma patients were or were not receiving bronchodilators. Similarly, 24-hour esophageal pH testing results did not show significant differences between asthma patients receiving versus those not receiving bronchodilators.⁹ Furthermore, Field et al⁷ noted that none of the asthma medications were associated with an increased likelihood of having heartburn or regurgitation. There is continued debate about the influence of bronchodilator medications on GER in asthma patients.

In summary, physiologic alterations associated with asthma may promote GER, which may partially explain the increased prevalence of GER in patients with asthma.

AIRWAY RESPONSES TO ESOPHAGEAL ACID

If GER triggers asthma, then esophageal acid should cause airway responses. Three pathophysiologic mechanisms have been proposed examining esophageal acid-induced bronchoconstriction, including (1) a vagal-esophageal-bronchial reflex, (2) heightened bronchial reactivity, and (3) microaspiration of esophageal contents into the upper airway. Also, esophageal acid may increase minute ventilation and respiratory rate without bronchoconstriction.

Vagal responses

The tracheobronchial tree and the esophagus share common embryonic foregut origins and autonomic innervation through the vagus nerve.²⁵ In a dog model Mansfield and Stein²⁶ noted that esophageal acid caused an increase in respiratory resistance that was ablated by bilateral vagotomy. In human studies Mansfield et al²⁷ noted that esophageal acid caused a 10% increase in asthma patients who had a positive Bernstein test result. Wright et al²⁸ studied 136 individuals and found significant reductions in airflow and arterial oxygen saturation after esophageal acid infusion. Atropine pretreatment abolished these findings, providing more evidence for an acid-induced vagally mediated esophagobronchial reflex.²⁸ Furthermore, by use of esophageal infusions in 4 groups (asthma patients with GER, asthma patients, subjects with GER, and healthy controls), Schan et al²⁹ showed that esophageal acid caused a decrease in the peak expiratory flow rate (PEF) in all groups without evidence of microaspiration, implying that a vagally mediated reflex is involved. Esophageal mucosal inflammation, assessed by a positive Bernstein test result, was not required for the airway responses. Asthma patients with GER had a further decline in PEF and an increase in specific airway resistance despite esophageal acid clearance. Interestingly, in a similar set of experiments using esophageal infusions in the supine position, microaspiration was not necessary for the PEF response, and specific airway resistance continued to increase (27% over baseline) 40 minutes after esophageal acid clearance in

asthma patients with GER.³⁰ Vagolytic doses of atropine partially ablated this response, further implying the importance of a vagally mediated reflex.³¹ The concept that microaspiration is not necessary to produce airway responses is also supported by Gastal et al,³² who noted that distal esophageal acid exposure is more prevalent than is proximal esophageal acid exposure, a prerequisite for microaspiration, in asthma patients. Autonomic dysregulation is also mediated through the vagus nerve, further implying a vagally mediated mechanism.

Heightened bronchial reactivity

Esophageal reflux may also cause neural enhancement of bronchial reactivity. Herve et al³³ examined the effect of esophageal acid on voluntary isocapnic hyperventilation of dry air and methacholine inhalation challenge. In patients with asthma esophageal acid infusions markedly potentiated bronchoconstriction induced by voluntary isocapnic hyperventilation compared with normal saline solution infusions ($P < .001$). Similarly, the dose of methacholine required to produce a 20% fall in FEV₁ (PD₂₀) was significantly decreased with esophageal acid infusion compared with saline solution ($P < .01$). This study shows that esophageal acid alters underlying bronchial reactivity to other stimuli. Vagal pathways are also important in this mechanism because the bronchial response to esophageal acid was abolished with atropine pretreatment.³³ Furthermore, a study of 105 consecutive asthma patients showed that the methacholine PD₂₀ correlated with number of reflux episodes on 24-hour esophageal pH testing.¹³ These data suggest that esophageal acid augments airway hyperresponsiveness.

Microaspiration

Tuchman et al³⁴ examined airway responses of esophageal acid (reflex mechanism) to tracheal acid (microaspiration mechanism) in a cat model, observing that 10 mL of esophageal acid caused a 1.5-fold increase in total lung resistance compared with nearly a 5-fold increase after 0.5 mL of tracheal acid. Furthermore, the esophageal acid response occurred in only 60% of the animals versus 100% with tracheal acid. The effect of tracheal acidification on total lung resistance was abolished with bilateral cervical vagotomy, so that even in the microaspiration model the vagus nerve plays a significant role.³⁴

In humans Jack et al³⁵ monitored tracheal and esophageal pH simultaneously in patients with severe asthma. Thirty-seven episodes of esophageal reflux were observed, with 5 of these episodes associated with a fall in tracheal pH. Peak expiratory flow rate decreased 84 L/min when both esophageal and tracheal acid were present versus only 8 L/min when esophageal acid alone was present. Episodes of tracheal microaspiration were associated with significant deterioration in pulmonary function.

Furthermore, in an animal model Sant'Ambrogio et al³⁶ noted that acid-pepsin laryngeal instillations impaired the airway patency-maintaining mechanisms of

pig model Hamamoto et al⁴¹ found that esophageal acid releases substance P and that this release of substance P was coupled with airway edema. The airway edema was potentiated by inhibiting neutral endopeptidase, an enzyme responsible for inhibiting tachykinins. Also, the airway edema was inhibited by FK-888, a substance P receptor antagonist. These findings led to the conclusion that esophageal acid releases tachykinins, including substance P, from sensory neurons, resulting in airway edema. The neural pathway seemed to involve both vagal pathways and local axon reflexes (Fig 1).⁴¹ In this model the esophagus was isolated so that microaspiration could not occur.

ASTHMA OUTCOME WITH ANTIREFLUX THERAPY

If GER triggers asthma, then adequate control of GER should improve asthma outcome. Some of the more recent medical and surgical trials evaluating asthma outcome are reviewed below.

Medical therapy

Many therapeutic trials performed have study design limitations, including the absence of a control group, small selected patient populations, inconsistent outcome parameters, and lack of objective evidence of acid suppression. More important, many therapeutic trials were too short to adequately assess asthma outcome, and many trials used a placebo-cross-over design. Despite these limitations, many studies show modest improvement in asthma symptoms, and in some studies objective improvement in pulmonary function. Recently, trials using proton pump inhibitors, which directly inhibit gastric acid secretion, have evaluated asthma outcome.⁴² Meier et al⁴³ 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 nonresponders, 6 (45%) had esophagitis, and the nonresponders 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.⁴³ Furthermore, Ford et al⁴⁴ examined 11 nocturnal asthma patients with GER, comparing 4 weeks of omeprazole 20 mg a day with placebo in a randomized double-blind placebo-controlled cross-over trial, finding no change in asthma symptoms, bronchodilator use, or PEF. Teichtahl et al⁴⁵ also reported a randomized placebo-controlled cross-over trial of 20 nocturnal asthma patients with omeprazole 40 mg a day for 4 weeks. Gastroesophageal reflux symptoms improved on therapy, but patients who underwent pH testing had no decrease in esophageal acid exposure. A small but statistically significant improvement in evening PEF was seen; however, asthma symptoms, β_2 -agonist use, morning PEF, and spirometry did not change.⁴⁵ In yet another study Boeree et al⁴⁶ reported a double-blind placebo-controlled

trial in 30 asthma patients with GER using omeprazole 40 mg twice daily for 3 months. Unfortunately, there was difficulty with patient compliance with 13 (43%) subjects who took less than 75% of their study drug. Spirometry, PEF, methacholine PD₂₀, asthma symptom scores, and medication use were not improved with antireflux therapy.⁴⁶

Harding et al¹ performed a prospective pretest-posttest evaluation of 30 asthma patients with GER using 3 months of acid-suppressive therapy. Seventy-three percent of asthma patients with GER had at least 20% improvement in PEF or a decrease in asthma symptoms. Acid-suppressive therapy required more than 20 mg of omeprazole a day in 27% of patients. Asthma symptoms required time to improve. After 1 month of acid-suppressive therapy, there was a 30% reduction in asthma symptoms, at 2 months a 43% reduction, and at 3 months a 57% reduction in asthma symptoms compared with baseline. There was also an improvement in FEV₁, FEV₁/forced vital capacity, and midexpiratory flow rates in asthma symptom responders.¹

Recently, Field and Sutherland⁴⁷ reviewed all English language studies from 1966 to 1996 in the MEDLINE database evaluating asthma outcome with medical GER therapy. Twelve peer-reviewed studies identified 326 treated subjects. They noted that asthma symptoms improved in 69% of subjects and asthma medications were reduced in 62% of subjects. Evening PEF improved in 26% of subjects. When pulmonary function was evaluated, none of the studies showed significant improvement. The authors concluded that GER therapy improves asthma symptoms and likely decreases the need for asthma medications; however, pulmonary function may not improve.⁴⁷ A double-blind placebo-controlled multicenter trial evaluating asthma outcome with aggressive medical therapy with use of a proton pump inhibitor has not been reported to date.

Surgical trials

Surgical trials have also evaluated asthma outcome. Of 110 carefully selected patients with asthma and GER undergoing antireflux surgery in combined trials, 34% were free of asthma symptoms after surgery and 42% showed an improvement in symptoms.⁴ Many patients were able to discontinue asthma medications. Unfortunately, the majority of surgical trials have design flaws, including the lack of a control group, poor documentation of airflow obstruction before and after the surgery, poor documentation of asthma medication use, and no documentation that GER was adequately controlled in the postoperative state.⁴ Spivak et al⁴⁸ reviewed a database of more than 600 patients and identified 39 asthma patients with GER and asthma who underwent fundoplication. Asthma symptom and medication scores decreased significantly after antireflux surgery, with 7 of 9 (78%) patients able to discontinue oral corticosteroids. Hunter et al⁴⁹ examined laparoscopic fundoplication outcome in 300 patients, of whom 10 had asthma and of whom 85% had asthma improvement. Finally, Johnson

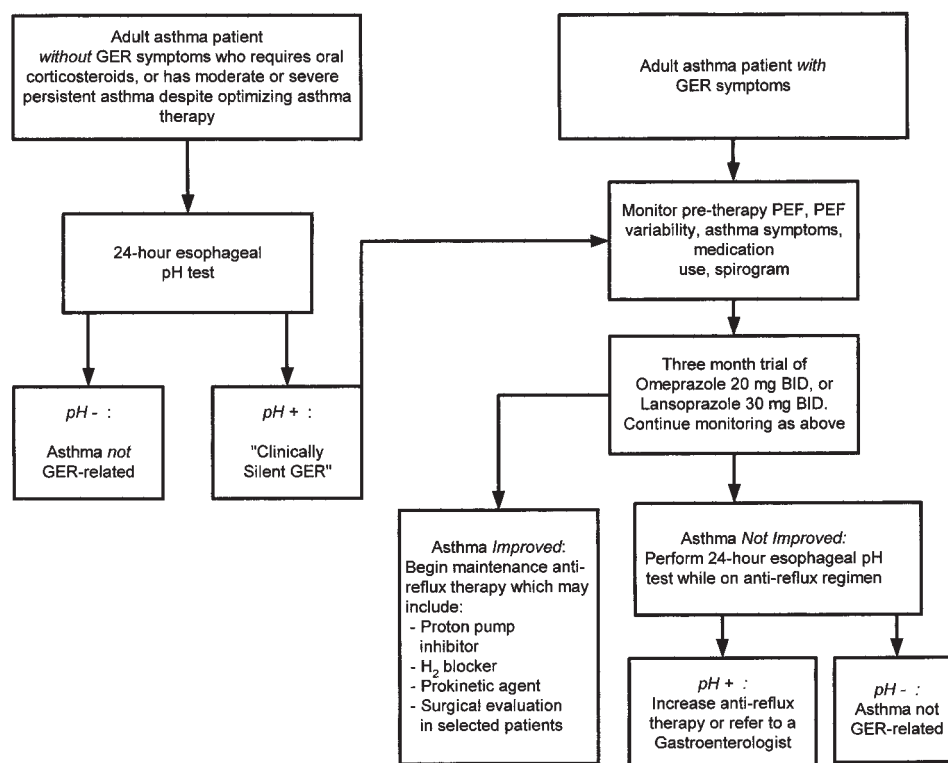


FIG 2. Proposed management approach to gastroesophageal reflux in adult patients with asthma. *pH+*, Positive esophageal pH test; *pH-*, negative esophageal pH test; *BID*, twice daily.

et al⁵⁰ examined respiratory symptoms after antireflux surgery and found improvement in 76% of patients.

Asthma outcome in medically versus surgically treated patients

Two studies performed before the advent of the proton pump inhibitors evaluated asthma outcome in a placebo-controlled manner comparing medical and surgical therapy. Larrain et al⁵¹ conducted a prospective, randomized trial in 81 nonallergic asthma patients with GER. Minimum follow-up was 6 months. Patients received placebo, cimetidine 300 mg 4 times daily, or the Hill antireflux surgical repair for GER. Asthma symptoms improved in all 3 groups, with the greatest improvement seen in the 2 treatment groups. Asthma symptoms scores improved by 77% in the surgical group, 74% in the cimetidine group, and 36% in the placebo group.⁵¹ There was no change in objective measures of airflow obstruction, including FEV₁. This study did not monitor PEF rates and did not report asthma severity. Medication use scores also decreased significantly in the treatment groups compared with the placebo group. Sontag et al⁵² performed a prospective randomized placebo-controlled trial comparing ranitidine 150 mg 3 times daily versus surgery with a Nissen fundoplication in 73 asthma patients with GER, with duration of follow-up as long as 5 years. Asthma was considered improved or cured in 75% of patients in the surgically treated group compared with 9% of

patients in the ranitidine group and 4% in the placebo group. In the surgery-treated group 33% of patients were able to discontinue oral corticosteroid therapy compared with 11% in the ranitidine group and none in the placebo-treated group. The 70% to 80% asthma symptom improvement rate of antireflux surgery parallels the 70% improvement in asthma outcome with proton pump inhibitors.¹

PREDICTORS OF ASTHMA RESPONSE

Harding et al¹ examined predictors of asthma response by comparing variables in asthma symptom responders and nonresponders in a prospective study. In a forward stepwise logistic regression analysis examining models to predict asthma outcome, the presence of regurgitation more than once a week or excessive amounts of proximal esophageal reflux (defined as a percentage of time that esophageal pH was less than 4 >1.1% of the time) predicted at least a 20% improvement in asthma symptoms. These 2 predictors had a 100% sensitivity, a 100% negative predictive value, a specificity of 44%, and a positive predictive value of 79%. The finding that abnormal amounts of proximal esophageal acid predicted asthma response was reproduced by Schnatz et al,⁵³ who noted that 4 of 4 (100%) subjects with proximal-only reflux had a favorable response to antireflux therapy. Also, 9 of 11 (82%) with distal esophageal reflux only had a favor-

able response. None of the 5 patients with normal esophageal acid contact times had pulmonary improvement with antireflux therapy.⁵³

Other studies have reported possible predictors of asthma response. For example, Meier et al⁴³ found that only patients with endoscopic healing of esophagitis had asthma improvement ($P < .01$). Larrain et al⁵¹ performed a trial on a subset of nonallergic asthma patients with less than grade 1 esophagitis who had asthma improvement. Irwin et al¹⁵ reported asthma improvement in difficult-to-control asthma patients. Ekström et al⁵⁴ found that a history of reflux-associated respiratory symptoms predicted asthma improvement in 48 patients with moderate-to-severe asthma.

Surgical studies have also evaluated predictors of asthma response. Perrin-Fayolle et al⁵⁵ reported predictors of asthma response in 44 asthma patients with GER more than 5 years after surgery. Younger patients and those with nocturnal asthma or intrinsic asthma had asthma improvement. The onset of GER symptoms before respiratory symptoms, severe GER, and response to medical antireflux therapy predicted asthma improvement. DeMeester et al⁵⁶ performed fundoplication in medical nonresponders and found that patients with normal esophageal motility and pulmonary symptoms during or within 3 minutes of reflux had higher success rates. More recently, Hunter et al⁴⁹ showed that asthma response to medical antireflux therapy predicted asthma response to fundoplication at 1 year follow-up. Johnson et al⁵⁰ noted that normal esophageal motility predicted a favorable outcome.

In conclusion, there are many predictors of asthma response, including the presence of regurgitation more than once a week, the presence of proximal reflux on esophageal pH testing, the presence of nocturnal asthma, the presence of reflux-associated respiratory symptoms, the presence of nonallergic asthma, the presence of less than grade 1 esophagitis, and healing of esophagitis with antireflux therapy. Favorable outcome was also noted in difficult-to-control asthma (patients requiring more than 10 mg of prednisone every other day). In surgical studies normal esophageal motility and asthma improvement with medical antireflux therapy predicted improved asthma outcome.

POSSIBLE MANAGEMENT APPROACH IN ADULT ASTHMA PATIENTS WITH GER

On the basis of current information, the following algorithm may be considered in adult asthma patients with GER. The clinician should inquire about reflux symptoms in all patients. If reflux symptoms are present, then a therapeutic trial of aggressive acid suppression should be attempted to examine asthma outcome as outlined in Fig 2.

Twenty-four-hour esophageal pH testing was abnormal in 72% of asthma patients with reflux symptoms.¹⁴ Although reflux symptoms are not 100% specific or sensitive for the presence of GER, a therapeutic trial to see whether asthma is GER related is reasonable in asthma

patients with GER symptoms. On the contrary, some asthma patients with GER may not have reflux symptoms, so GER is "clinically silent."^{14,15} In difficult-to-control asthma or in moderate-persistent or severe-persistent asthma without reflux symptoms, 24-hour esophageal pH testing should be considered. Unfortunately, demographic variables do not predict which patients without reflux symptoms have positive esophageal pH tests, so pH testing is required to identify these individuals.¹⁴ Other tests for GER should be considered in patients who plan to undergo fundoplication or in patients who have esophageal complications of GER and it should be performed by a competent gastroenterologist.

Although there have been no extensive studies evaluating cost-effectiveness, O'Connor et al⁵⁷ designed a disease model examining strategies for diagnosing GER-related asthma. Preliminary results show that the most cost-effective strategy was empiric omeprazole for 3 months followed by 24-hour esophageal pH testing in the nonresponders to include or exclude GER as an exacerbating factor in asthma.⁵⁷ Because GER is a chronic and unrelenting disease, aggressive therapy may be a lifetime commitment. Currently, there are no studies available that directly compare the cost-effectiveness of medical versus surgical therapy for GER-related asthma. Benefits of medical therapy include its ease of initiation, reversibility, relatively low risk, and widespread availability. Disadvantages include the need for daily medication and the lifetime cost of therapy. Laparoscopic fundoplication has made surgery an attractive approach. Long-term recurrence rates of laparoscopic procedures have not been determined but are thought to be similar to those of open procedures. The primary benefit of surgery includes the possibility for permanent therapy of GER with a one-time cost of approximately \$15,000 to \$20,000.⁴ Further clinical studies are needed for specific recommendations concerning maintenance therapy of GER in asthma patients with GER.

CONCLUSION

Gastroesophageal reflux is a potential trigger of asthma, and aggressive reflux therapy improves asthma symptoms in approximately 70% of asthma patients with GER. GER prevalence in asthma patients approaches 80%. In asthma patients with GER, many respiratory events are associated with esophageal acid. Pathophysiologic mechanisms of esophageal acid-induced bronchoconstriction include a vagally mediated reflex, heightened bronchial reactivity, and microaspiration. Esophageal acid may also be associated with an increase in minute ventilation. In a guinea pig model esophageal acid induced substance P release, which was associated with airway edema.

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. Not all asthma patients with GER have esophageal symptoms,

and 24-hour esophageal pH testing is required to identify GER in these "clinically silent" patients. Further clinical investigations will further delineate the association between GER and asthma.

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