CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will treat asthma exacerbations in the light of recent evidence that seems to conflict with current guidelines

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Treating silent reflux disease does not improve poorly controlled asthma

ABSTRACT

Many patients with asthma also have gastroesophageal reflux disease (GERD), and GERD can cause symptoms that mimic those of poorly controlled asthma. Patients with poorly controlled asthma are often treated empirically for GERD, whether or not they have symptomatic reflux. However, a randomized, placebo-controlled trial funded by the American Lung Association and the National Institutes of Health found that treating silent GERD does not improve asthma control. These results warrant a reevaluation of current guidelines and clinical practice.

KEY POINTS

Acid reflux is more prevalent in patients with asthma, and it often occurs without classic symptoms such as heartburn.

Current guidelines, based on data from older studies with significant limitations, recommend considering treatment for reflux disease, even without the classic symptoms, in patients with uncontrolled asthma.

The recent Study of Acid Reflux in Asthma found not only that treating silent acid reflux does not improve asthma control, but also that esophageal pH monitoring does not detect a subgroup of asthma patients who might respond to a proton pump inhibitor. These data suggest that we should reconsider clinical practice based on current guidelines.

Dr. Parsons has received honoraria from GlaxoSmithKline, Merck, and AstraZeneca.

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Should patients with poorly controlled asthma be treated empirically for gastroesphageal reflux disease (GERD)?

Current guidelines[1] indicate that trying a proton pump inhibitor may be worthwhile. However, the results of a recent multicenter trial[2] indicate that this does not help control asthma symptoms and that we need to reevaluate the guidelines and focus on other factors that can worsen asthma control.

REFLUX DISEASE IS LINKED TO ASTHMA

GERD's association with asthma has long been recognized. Asthma patients have a higher prevalence of GERD than the general population, with reported rates of 20% to 80%.[3–8]

GERD may worsen asthma via several mechanisms. If stomach acid gets into the airway, it can induce bronchoconstriction, vagal reflexes, and chronic airway inflammation, all of which can increase airway reactivity.[9–16] Chronic reflux can also cause inflammation of the esophagus, which can exacerbate cough and possibly bronchospasm via neurogenic mechanisms.[17]

In turn, asthma may worsen GERD. Airway restriction can lead to hyperinflation and increased negative inspiratory pleural pressure, both of which may reduce the effectiveness of the lower esophageal sphincter.[18] In addition, the beta-agonists and methylxanthines used to treat asthma may impair function of the lower esophageal sphincter and exacerbate reflux.[18–20]

CURRENT GUIDELINES ARE BASED ON LIMITED INFORMATION

The symptoms of GERD and asthma are nonspecific and can be similar (chest tightness,

TABLE 1

Previous studies of proton pump inhibitor therapy and asthma control

STUDY	NO. OF PATIENTS	HOW GERD WAS DIAGNOSED	PPI AND DOSING	DURATION	RESULT
Ford et al,[21] 1994	11	Endoscopy pH probe	Omeprazole (Prilosec) 20 mg/day	4 weeks	No effect
Teichtahl et al,[22] 1996	20	Endoscopy pH probe	Omeprazole 40 mg/day	4 weeks	3% increase in morning peak expiratory flow rate
Meier et al,[23] 1994	15	Endoscopy pH probe	Omeprazole 20 mg twice daily	6 weeks	29% of patients had increased FEV_1
Harding et al,[24] 1996	30	Symptoms pH probe	Omeprazole titrated (mean dose 27 mg/day)	3 months	67% had symptom response 20% had increase in morning peak expiratory flow rate
Levin et al,[25] 1998	9	pH probe	Omeprazole 20 mg/day	8 weeks	Improved peak expiratory flow rate and quality of life
Boeree et al,[26] 1998	18	pH probe	Omeprazole 40 mg twice daily	12 weeks	No effect
Kiljander et al,[27] 1999	57	pH probe	Omeprazole 40 mg/day	8 weeks	35% had symptom response
Littner et al,[29] 2005	207	Symptoms Clinician diagnosis pH probe (optional)	Lansoprazole (Prevacid) 30 mg twice daily	24 weeks	Mixed (see text)
Kiljander et al,[28] 2006	770	Symptoms History of abnormal pH probe History of abnormal endoscopic study	Esomeprazole (Nexium) 40 mg twice daily	16 weeks	Improved peak expiratory flow rate in those with symptoms of nocturnal asthma and acid reflux

GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor; FEV_1 = forced expiratory volume in the first second of expiration

chest discomfort), which can make it challenging for clinicians or patients to distinguish asthma from GERD.[2] Moreover, in asthma patients, GERD often presents without classic symptoms such as heartburn, and thus has been labeled "silent" GERD.

Earlier studies[21–29] (TABLE 1) suggested that treating GERD may improve asthma control. Based on this information, the most recent asthma guidelines from the National Institutes of Health (NIH) recommend trying GERD treatment in patients with poorly controlled asthma, even if they do not have classic GERD symptoms.[1]

However, these studies all had significant limitations, such as small sample size. Also, the definitions of asthma and GERD differed from study to study. In some cases, the definition of GERD included self-reported GERD, which often fails to correlate with GERD documented with esophageal pH monitoring in asthma patients.[1] These limitations were highlighted in a Cochrane review,[30] which found that asthma patients with GERD showed no overall improvement in asthma after treatment of reflux. It concluded that small groups of patients may benefit, but that predicting who will respond is difficult.

Larger randomized controlled trials[28,29] attempted to address some of these limitations,

with varying results.

Littner et al[29] gave lansoprazole (Prevacid) 30 mg twice daily or placebo to 207 patients with moderate to severe asthma and symptomatic GERD and saw no improvement in daily asthma symptoms, ie, asthma control in the active-treatment group. While these patients had an improvement in symptoms of severe reflux, their overall quality-of-life scores were similar to those of the placebo group. Of note, patients needing more than one type of drug for asthma control had a lower rate of asthma exacerbations.

Kiljander et al[28] gave esomeprazole (Nexium) 40 mg twice daily or placebo to 770 patients who had mild to moderate asthma and symptoms of nocturnal asthma with or without symptoms of GERD. The only benefit was a slight improvement in peak expiratory flow in those with symptoms of both GERD and nocturnal asthma, and this was most significant in patients taking long-acting beta-agonists. Other measures—eg, the forced expiratory volume in the first second (FEV_1), use of a beta-agonist, symptom scores, and nocturnal awakenings—did not improve.

In both of these studies,[28,29] patients reported symptoms of GERD, so they did not have silent GERD.

THE DESIGN OF SARA

To address the limitations of the studies discussed above and evaluate the effect on asthma control of treating silent GERD, the American Lung Association and the National Heart, Lung, and Blood Institute funded the multicenter Study of Acid Reflux in Asthma (SARA) (TABLE 2).[2]

In SARA, 412 patients age 18 and older with inadequately controlled asthma were randomized to receive esomeprazole 40 mg twice a day or placebo for 24 weeks. Inadequate control was defined as a score of 1.5 or higher on the Juniper Asthma Control Questionnaire[31] despite treatment with inhaled corticosteroids. Patients had no symptoms of GERD. The 40-mg twice-daily dosage of esomeprazole was chosen because it is known to suppress more than 90% of acid reflux.[24,32]

All patients completed a baseline asthma diary, recording peak expiratory flow rates, asthma symptoms, nighttime symptoms, and beta-agonist use. This information was collected every 4 weeks throughout the trial.

All participants also underwent esophageal pH monitoring for an objective confirmation of GERD. Patients were randomized independently of the results of the pH probe; in fact, investigators and patients were blinded to these results.

The primary outcome measure was the rate of episodes of poor asthma control, with poor control defined as any of the following:

- A decrease of 30% or more in the morning peak expiratory flow rate on 2 consecutive days, compared with the patient's best rate during the run-in period

TABLE 2

The Study of Acid Reflux in Asthma: An overview

Population
412 participants (age ≥ 18) at 19 centers

Patients with asthma inadequately controlled despite using inhaled corticosteroids but with no symptoms of acid reflux, randomly assigned to esomeprazole (Nexium) 40 mg twice daily or placebo, for 24 weeks

Initial evaluation
Asthma diagnosed by a physician, plus either a positive methacholine challenge test or a positive bronchodilator response to an inhaled beta-agonist

Acid reflux confirmed by ambulatory esophageal pH monitoring, with episodes and severity measured by the Gastroesophageal Reflux Disease Symptom Assessment Scale

Randomization
Patients randomized independently of the results of pH monitoring; investigators and participants blinded to the results of pH monitoring

Follow-up
Participants kept a diary, recording peak expiratory flow rates, asthma symptoms, nighttime symptoms, and beta-agonist use; every 4 weeks the diary data were reviewed and spirometry was done

Results
No treatment effect with respect to episodes of poor asthma control or with respect to secondary outcomes, including pulmonary function, airway reactivity, asthma control, symptom scores, nocturnal awakening, or quality of life

Subgroup analysis failed to identify any group that benefited from proton pump inhibitor therapy, including those with acid reflux documented with pH monitoring or those taking a long-acting beta-agonist

- An urgent visit, defined as an unscheduled health care visit, for asthma symptoms
- The need for a course of oral prednisone for treatment of asthma.

Asthma was defined as doctor-diagnosed, plus either a positive methacholine challenge test (a concentration of methacholine causing a 20% reduction in FEV_1 [PC_{20}] < 16 mg/mL) or a positive bronchodilator response (a 12% increase in FEV_1) to an inhaled beta-agonist. Participants had no other indication for acid suppression, including symptoms of GERD or previously diagnosed erosive esophageal or gastric disease.

Acid reflux was evaluated by ambulatory pH monitoring, which had to last at least 16 hours and span one meal and 2 hours in the recumbent position. Reflux was present if the pH was less than 4.0 for more than 5.8% of total time, 8.2% of time upright, or 3.5% of time lying down.[33] Episodes and severity were measured by the Gastroesophageal Reflux Disease Symptom Assessment Scale.[34]

SARA RESULTS: NO IMPROVEMENT IN ASTHMA WITH GERD TREATMENT

Current guidelines that suggest empirically treating GERD in asthma patients may need to be reevaluated

The SARA treatment and control groups had similar baseline characteristics, with similar asthma symptoms. Most of the patients were women: 72% of the placebo group and 64% of the esomeprazole group. Most had baseline spirometric results at the lower end of normal (the mean FEV_1 was 76% ± 16 SD in the treatment group and 78% ± 15 in the placebo group) and had very poor asthma control, with an average Juniper Asthma Control Questionnaire score of 1.9 (> 1.5 is considered poor control).[31] GERD was documented with esophageal pH monitoring in 40% of patients, showing that a significant number had silent GERD.

Episodes of poor asthma control occurred with similar frequency in the esomeprazole and placebo groups (2.5 vs 2.3 events per person-year, $P = .66$). Treatment made no difference in this end point regardless of the baseline results of pH monitoring. No treatment effect was noted in the individual components of the episodes of poor asthma control or in secondary outcomes, including pulmonary function, airway reactivity, asthma control, symptom scores, nocturnal awakening, or quality of life.

In addition, subgroup analysis failed to identify any group—including those with documented reflux on pH probe testing or those receiving a long-acting beta-agonist—who benefited from proton pump inhibitor therapy.

The investigators concluded that these data suggest treatment of silent GERD does not improve asthma control and thus that a reevaluation of current guidelines and clinical practice is warranted.[2]

ISSUES REMAIN

This large clinical trial, in which asthma and GERD were well defined and objectively measured, was robustly negative in terms of showing any benefit of treatment of silent GERD on asthma control. The study population was representative of those for whom such a treatment is recommended in the current NIH guidelines, which are based on data published prior to SARA.

However, while SARA was well designed and had clear results, it had some limitations, and some issues regarding GERD and asthma remain unanswered.

Is acid the only problem in GERD? SARA focused on acidic GERD. Aspiration of substances such as pancreatic enzymes, pepsin, and bile has also been shown to induce symptoms in asthma patients.[2,32,35] In addition, distention of the esophagus and stimulation of neurogenically mediated reflexes can cause symptoms or neurogenic airway inflammation that is not mitigated by drugs that target acid reflux.[32]

Indirectly supporting this theory is evidence that surgical interventions such as fundoplication can improve asthma symptoms.[36] However, this evidence is only from small studies with significant limitations.

Is proximal GERD worse than distal GERD? SARA did not address whether proximal and distal reflux may affect asthma differently. The importance of proximal reflux in asthma has not been clearly established, but there is evidence that patients with proximal GERD have a higher incidence of nocturnal cough than patients who have only distal reflux.[37]

Dimango et al[38] recently reported ad-

ditional data from SARA in which patients with poorly controlled asthma underwent both proximal and distal esophageal pH monitoring to see if proximal GERD was associated with poor asthma control: 304 patients underwent dual pH-probe assessment and 38% of them had proximal reflux. The authors found no difference between those with and without proximal GERD with regard to nocturnal awakenings, need to use a rescue inhaler, inhaled controller medication dose, lung function, or airway reactivity by methacholine challenge. However, they did find that those with proximal GERD had worse asthma quality-of-life scores, and worse health-related quality-of-life scores and were more likely to complain of cough.

Thus, it appears that proximal GERD may worsen quality of life in asthmatic patients but does not worsen asthma control.

SARA RESULTS: IMPLICATIONS FOR MANAGEMENT

The SARA results suggest that patients with poorly controlled asthma who are on adequate controller medications should not be treated empirically for silent GERD in the expectation that the asthma will improve. Rather, they suggest that the focus should be on other factors that can worsen asthma control, such as the ability to properly use an inhaler, the ability to afford medications, compliance with drug treatment, and adequate control of other significant comorbidities such as allergic bronchopulmonary aspergillosis, sinusitis, allergic rhinitis, vocal cord dysfunction, and occult heart disease. The most recent NIH guidelines also suggest considering referral to an asthma specialist if symptoms persist despite adequate controller therapy.

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CORRECTION (DRUG NAME ERROR)

Diffuse alveolar hemorrhage

(APRIL 2008)

A incorrect brand name was used for a formulation of methyprednisolone in: Ioachimescu OC, Stoller JK. Diffuse alveolar hemorrhage: Diagnosing it and finding the cause Cleve Clin J Med 2008; 75:258–280; doi:10.3949/ccjm.75.4.258. On page 275, in the section on treatment, the second paragraph should read:

"Most experts recommend intravenous methylprednisolone (Solu-Medrol) (up to 500 mg every 6 hours, although lower doses seem to have similar efficacy) for 4 or 5 days, followed by a gradual taper to maintenance doses of oral steroids."

The online versions of this article have been corrected.

CORRECTION

Renal stone interventions

(OCTOBER 2009)

A typographical error appeared in: Samplaski MK, Irwin BH, Desai M. Less-invasive ways to remove stones from the kidneys and ureters. Cleve Clin J Med 2009; 76:592–598. On page 594, second column, fourth paragraph, the text should read, "Lithotripsy is more likely to fail if the skin-to-stone distance is more than 10 cm…"—not 10 mm.

CME ANSWERS Answers to the credit tests on page 215 of this issue

Reflux and asthma **1B 2E**
Liver enzymes **1B 2E**
Renal artery stenosis **1D 2A**
Measles **1D 2A**