Gastroesophageal reflux disease and childhood asthma

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Purpose of review
Gastroesophageal reflux disease (GERD) is common in children with asthma and may be present with or without symptoms. Clinicians, influenced by position statements in national guidelines, have routinely treated children with poorly controlled asthma with various anti-GERD medications. This practice is based on the pervasive but unproven belief that GERD is an important determinant of poor asthma control.

Recent findings
Clinical studies show that GERD is highly prevalent in children with asthma, with estimates as high as 80%, but nearly half of the children are asymptomatic. However, there is no conclusive evidence per se that asymptomatic GERD informs asthma control, and treatment of GERD in the few controlled trials available for review does not substantively improve asthma outcomes. In a recent large controlled clinical trial, treatment with a proton-pump inhibitor (PPI) was not only ineffective, but adverse effects were common, including an increased prevalence of symptomatic respiratory infections.

Summary
Current evidence does not support the routine use of anti-GERD medications in the treatment of poorly controlled asthma of childhood. However large controlled trials of children symptomatic of both GERD and asthma have not been conducted, and in this case the benefits of treatment, although unproven, might outweigh the risks.

Keywords
asthma, gastroesophageal reflux disease, lansoprazole, pH monitoring studies, proton-pump inhibitors

INTRODUCTION
Gastroesophageal reflux (GER), the intermittent ascent of gastric contents into the esophagus, is a normal physiological process. At least 40% of normal-term infants regurgitate every day [1]. However, when episodes of GER are frequent and associated with troublesome symptoms, gastroesophageal reflux disease (GERD) is present and can lead to serious complications including esophagitis [2]. Osler in 1892 [3] postulated the now pervasive belief that GERD is an important cause of morbidity in patients with asthma.

US guidelines tout gastroesophageal reflux disease as an important cause of poor asthma control
The current US guidelines for the treatment of asthma state GER should be treated in patients with asthma and symptomatic GERD [4], but it is not clear whether such treatment improves asthma control. Furthermore the US guidelines also state that an investigation for GERD is indicated in patients with poorly controlled asthma. Indeed, GERD is highly prevalent in the general population [5], therefore GERD and asthma may be associated by chance alone and have no important pathophysiological interdependence.
KEY POINTS

- The prevalence of GERD identified by esophageal pH monitoring is high in children with asthma, and on average is 63% from published studies.
- However, most studies show no differential effect of asymptomatic GERD on determinants of asthma control in children treated with inhaled corticosteroids.
- Treatment of asymptomatic GERD with a PPI did not improve any metric of asthma control in children treated with inhaled corticosteroids in a large placebo controlled clinical trial.
- Symptomatic upper respiratory infections are more common in children with poorly controlled asthma on inhaled corticosteroids treated with FDA-approved doses of a PPI vs. placebo.
- Further clinical trials are indicated in children with concurrent GERD and poorly controlled asthma to test whether symptomatic GERD informs asthma control in a meaningful way, and whether combination therapy with PPI and pro-motility drug improves asthma control.

Gastroesophageal reflux disease and poor asthma control: proposed mechanisms

Two primary mechanisms have been proposed to explain the association of GERD with asthma [6]. It is known that the distal esophagus and trachea have pH-sensitive irritant receptors that when stimulated elicit bronchospasm [7] and increase airway hyperresponsiveness [8] through cholinergic pathways [9]. Likewise, microaspiration of gastric acid promoted by loss of protective upper airway reflexes may directly inflame the lower airways, but evidence of chronic aspiration as a common complication of asthma is indirect [10]. The situation is even more confusing in young children, who may be more prone to complications of GERD due to developmental immaturity of the gastroesophageal sphincter [11] and diminished airway protective reflexes. However, although such compensatory reflexes are depressed in the very young, an older study supports the view that risk of aspiration and loss of laryngeal responses to irritants is more common in older adults [12]. Furthermore, the tone in the distal esophagus as measured by resting lower esophageal sphincter pressure is actually higher in young children, and a low esophageal sphincter tone per se is not the sole determinant of GER in children [13]. Further studies establish that resting lower esophageal sphincter pressures are similar among preterm infants, term infants, and adults [14]. Thus, there is little evidence to support the generalized belief that children are more prone to GER due to immaturity of gastroesophageal sphincter function.

The symptoms of asthma are similar to the symptoms of gastroesophageal reflux disease

An important challenge in understanding the association between asthma and GERD in children is that both disorders have similar clinical signs and symptoms. Both can cause nocturnal cough and sleep disturbance. Likewise chest tightness, chest pressure, and chest pain are common to both. Patients with symptoms from asthma likely misuse GER medications and patients with similar symptoms from GER likely misuse short-acting asthma medications. In two large clinical trials, one in adults [15] and a second in children [16**], the mean number of gastrointestinal symptoms was nearly identical in participants with and without GERD identified by esophageal pH monitoring. Based on a validated gastrointestinal symptom assessment scale, only heart-burn differentiated a positive from a negative esophageal pH study in adults with poorly controlled asthma [15]. In children with poorly controlled asthma, no gastrointestinal symptom differentiated participants with and without GERD identified by esophageal pH monitoring [16**]. Thus, earlier interventional studies in both adults and children emphasizing symptom scores as primary or secondary end points are likely confounded by the inability of patients to differentiate symptoms of asthma from GER. Future trials should emphasize broader and more objective end points.

TEXT OF THE REVIEW

We identified 13 publications from 1989 to 2012, which included esophageal pH studies in the assessment of children with asthma (Table 1) [16**,17–28]. There were six interventional trials [16**,17–21], four cross-sectional studies [22–25], and three retrospective analyses [26–28]. All but two included less than 70 participants, and 10 studied children with poorly controlled or severe asthma. The age distributions were broad but tended to be skewed towards younger children.

Association of gastroesophageal reflux with asthma in children

The prevalence of GERD ranged from as low as 43% to as high as 87%. From these publications, 602 children with asthma underwent esophageal pH monitoring, and 385 had findings consistent with GERD, for a net prevalence of 64%. The prevalence
of GERD in the studies was determined significantly by the inclusion criteria. For example, in the largest clinical trial, children with known GER or who were on active GERD treatment were excluded from study, and this study had the lowest prevalence of GERD at 42% [16]. The five interventional trials had specific inclusion criteria for asthma, and the overall prevalence of GERD among children participating in those studies was relatively lower (57%) than it was among children participating in cross-sectional (63%) and retrospective (71%) evaluations.

It is important to differentiate symptomatic from asymptomatic GER when considering the overall prevalence of GER in children with poorly controlled asthma, who are using inhaled corticosteroids. In the largest prospective trial with strict inclusion criteria and a detailed subject characterization, the prevalence of asymptomatic or ‘silent’ GER was 42% [16]. This is similar to the prevalence found in a large prospective trial in adults with asthma, 40%, using similar inclusion criteria [15]. In neither study did the presence of asymptomatic GER at baseline differentiate in any meaningful way the level of asthma control as assessed by lung function, bronchial hyperresponsiveness, quality of life, or response to treatment with a PPI medication. Likewise, assessment of proximal vs. distal GER in adult participants with asymptomatic GER was not highly informative; patients with proximal reflux report significantly worse asthma and health-related quality life despite lack of physiologic impairment or increase in asthma symptoms [29].

### Effects of proton-pump inhibitor treatment on asthma outcomes in children with poorly controlled asthma

Prescriptions for proton-pump inhibitors (PPI) for the treatment of poorly controlled asthma have increased substantially in the past decade even though the US Food and Drug Administration (FDA) has not approved any PPI for the treatment of asthma symptoms. In recent years, the FDA reports an 11-fold increase in new prescriptions for very young children from 2002 to 2009 [30]. There were fewer new patient prescriptions, thus the rise in the number of prescriptions was likely due to children receiving these drugs chronically [30]. Indeed, there is no verified indication for use in over 75% of patients on long-term PPI treatment [31]. This phenomenon is labeled ‘therapeutic creep’ which is the use of a treatment with proven efficacy in one population, in another population for whom efficacy has not been proven [32].

Of the six studies evaluating PPI use for treatment of asthma in children, five have been either of small sample size, not blinded, uncontrolled, or used a combination of antireflux treatments making it difficult to determine the efficacy of PPI therapy [18,21,33–35]. In these five studies, children had a diagnosis of GERD or were being evaluated for GER [18,21,33–35]. In three nonrandomized, nonplacebo-controlled studies, treatment of GERD with a PPI reduced asthma exacerbations and permitted a reduction in asthma medication use [18,21,34]. However, all three of these studies were confined to a single center and group of investigators, thus limiting the generalizability of the results. More
recently, in 29 children with endoscopically proven GERD and difficult to treat severe asthma, single-blind treatment with esomeprazole for 12 weeks improved scores on the Childhood Asthma Control Test [36] (although a clinically meaningful difference for that metric has not yet been defined). In contrast neither FEV₁ nor peak expiratory flow variability were significantly affected by treatment and similar numbers of children required step-up or had a step-down of asthma therapy [33]. In the first randomized, placebo-controlled trial in 38 children, treatment of GERD with omeprazole had no significant effect on asthma endpoints [35]. The largest and most recently published trial (n = 306), conducted by the American Lung Association Asthma Clinical Research Centers, enrolled children with poorly controlled asthma despite treatment with fluticasone propionate of at least 176 µg per day and without symptoms of GER requiring treatment [16**]. Children were randomized in a double-blind manner to lansoprazole or placebo for 6 months. Evaluations of the childhood Asthma Control Questionnaire (Fig. 1) [37], episodes of poor asthma control, asthma-related quality of life, pulmonary function, or bronchial hyperresponsiveness demonstrated no differences between treatments. Even in the 115 children with a baseline 24-h esophageal pH-monitoring test adequate for interpretation, there were no differences between treatments and there were no differences in gastrointestinal symptoms between children with a positive pH probe test compared with those with a negative test. This study is important because it unequivocally proved the lack of benefit of PPI treatment for uncontrolled asthma symptoms in children who also do not have symptomatic GER.

**Proton-pump inhibitor-related adverse events in children with asthma**

Until the publication from the American Lung Association Asthma Clinical Research Centers trial, no previous study of children with asthma had reported PPI-related adverse events [16**]. In this trial, there was a concerning increase in upper respiratory tract infection, sore throat, and bronchitis (though not pneumonia) in lansoprazole vs. placebo-treated children. Only one other study, in children with GERD, identified increased risks of intestinal and respiratory infection associated with PPI or H₂ blocker treatment [38]. Although a recent meta-analysis of 31 trials has confirmed an association of PPI use with pneumonia, the FDA has not yet required a warning of the risk for pneumonia to be included in the label for PPIs [39]. Results from the Asthma Clinical Research Centers network trial [16**] also noted a trend for an increase in activity-related bone fractures in children treated with PPI compared with placebo (P = 0.06). The FDA does require warning labels for all available PPI products because of the well established risks for hip, wrist, and spine fractures associated with long-term PPI use [40,41].

Complicating the use of PPIs in children with asthma who have a clinical indication for treatment is the potential for underdosing or overdosing using standard approved dosages due to interindividual variations in the activity of metabolizing enzymes. Omeprazole, esomeprazole, lansoprazole, and pantoprazole are metabolized by cytochrome P450 (CYP)2C19 primarily and to a lesser extent by CYP3A [42]. The gene encoding CYP2C19 has well known polymorphisms that can significantly decrease or increase enzyme metabolizing activity resulting in overdosing or underdosing, respectively, and differences in Helicobacter pylori cure rates have been observed [42]. Though there are no data at present, it is possible that adverse effect risks also could be related to metabolizer status such that poor metabolizers who have increased and prolonged blood concentrations of PPIs would be predisposed to adverse effects such as, pneumonia. Pharmacokinetic data by CYP2C19 genotype do not yet exist to aid in determining the correct PPI doses for children. Commercially available FDA approved tests for CYP2C19 genotype exist but no genotype-related dosing recommendations have been established [42].

Thus, it is clear that the evidence does not support PPI treatment for uncontrolled asthma.

![FIGURE 1. Effects of lansoprazole vs. placebo on the Juniper asthma control quotient (ACQ) in children with poorly controlled asthma who are taking inhaled corticosteroids. There was no treatment effect observed at any of the monthly visits and no effect comparing the ACQ at baseline (pretreatment) to the final 6-month time point [16**].](image-url)
symptoms in children who do not also have symptomatic GER and the data are weak even in those children with identified GERD. In addition, as more PPIs come off patent and become available without a prescription, more children are likely to be treated without physician or pharmacist involvement in decision-making and the risk of adverse events is likely to increase.

CONCLUSION

Asymptomatic GER as identified by esophageal pH monitoring is highly prevalent in children with asthma but is not a clear determinant of physiological or incremental health-related impairment. The evidence is clear that treatment of asymptomatic GER with FDA-approved doses of PPI in school-age children with poorly controlled asthma who are taking inhaled corticosteroids does not improve asthma control. However, further studies in children with poorly controlled asthma complicated by symptomatic GERD may be beneficial. Supplemental therapies including pro-motility agents with effects apart from acid suppression have not been widely studied in children with asthma and GER.

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Conflicts of interest

W.G.T. receives more than $10 000 per year speaker fees from Merck and Co, and more than $10 000 per year speaker fees from Genentech. W.G.T. also receives support from the National Institutes of Health/National Heart Lung Blood Institute as a contributing investigator in an NIH Program Project Grant 1 PO1 HL101871-01A1 (Cellular S-nitrosothiol signaling in respiratory biology), Severe Asthma Research Program (1U10HL109250-1), and the AsthmaNet clinical trials program (sub-contract to Wake Forest University 1U10HL098103-01). Takada Pharmaceuticals provided lansoprazole and matching placebo for the SARCA trial. None of these outside interests had any input on the design or content of this literature review.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 86).


17. Landmark clinical trial in children demonstrating no benefit of PPI treatment in asymptomatic GERD.


This is an important review of physician prescribing practices in the United States with PPI in treating very young children.