

# Children, Asthma, and Proton Pump Inhibitors

## Costs and Perils of Therapeutic Creep

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CHILDREN WITH ASTHMA REPORT SYMPTOMS OF GASTROESOPHAGEAL reflux disease (GERD) more often than children without asthma.<sup>1</sup> Nevertheless, a systematic review of the child health literature, which included studies using pH probes and other objective assessment methods, concluded that the true nature of the association between GERD and asthma, their temporal relation, and the causal direction, remain unknown.<sup>2</sup> Moreover, the potential for antacid therapy to improve asthma symptoms in children with poorly controlled disease remains largely anecdotal. A small, randomized placebo-controlled trial showed no improvement in asthma status among children treated with omeprazole for 12 weeks.<sup>3</sup>

Despite this unimpressive evidence of a consistent role of GER/GERD in asthma morbidity, children with asthma are more likely than those without asthma to be treated with anti-GERD medications. For example, a population-based study<sup>4</sup> suggested that 13- to 14-year-old schoolchildren with asthma were more than 8 times more likely to be treated with anti-GERD therapy than those without asthma. Children with more severe asthma reported much more frequent symptoms consistent with GERD and, thus, were more likely to receive such therapy. It appears that the conclusion based on association studies that poor asthma control could be caused by GER/GERD has contributed to a marked increase in the use of anti-GERD medicines in these patients.

The perils and costs of this overuse of anti-GERD therapy are cogently examined by Holbrook and colleagues in this issue of JAMA.<sup>5</sup> Results of this appropriately powered randomized clinical trial show that among children with asthma but without symptoms of GERD whose asthma symptoms were poorly controlled with anti-inflammatory therapy, 24 weeks of treatment with the proton pump inhibitor (PPI) lansoprazole had no significant effect on any measure of asthma control, quality of life, lung function, or bronchial responsiveness compared with placebo. In a subset of the population in which the investigators performed 24-hour esophageal pH monitoring stud-

ies, 43% showed esophageal acid exposure greater than established thresholds, a striking prevalence in a population with no symptoms of GERD. However, lansoprazole was no more effective in this subgroup than in the entire sample. These results are in concordance with those of a similar study using esomeprazole in adults with poorly controlled asthma and with no or mild GERD symptoms.<sup>6</sup> It could be argued that these studies, by excluding patients with symptomatic GERD, could have missed the patients most likely to respond to PPIs. However, a large study in adults with poorly controlled asthma and moderately severe GERD symptoms showed no effect of esomeprazole on the primary outcome (morning peak flow) or on most other clinical outcomes, with minor improvement in asthma quality of life that were considered of minimal clinical significance by the authors.<sup>7</sup>

Holbrook et al<sup>5</sup> also report that several unwanted adverse effects were observed more frequently in the active treatment group than in the placebo group. Treatment with lansoprazole was associated with increased incidence of upper respiratory tract infection, sore throat, and bronchitis. This finding is consistent with reports of increased risk of pneumonia associated with PPI therapy.<sup>8</sup> However, this increased risk of respiratory illnesses, which are a major cause of asthma exacerbations,<sup>9</sup> was not associated with a significantly increased incidence of episodes of poor asthma control in these children.

Of much greater concern is the difference in activity-related bone fractures in children treated with lansoprazole vs placebo (6 vs 1, respectively). This is the first large, blinded, randomized placebo-controlled trial in which this potential complication of PPIs has been studied in children; most available child health studies of PPIs are small, uncontrolled, and of short duration.<sup>10</sup> It is unlikely that the use of inhaled corticosteroids explains this finding because there was no difference in the use of these medicines between the 2 groups of patients. Although the increased fracture risk did not reach formal, 2-sided statistical significance ( $P=.06$ ), this finding should be considered in the framework of a substantial body of evidence that has prompted the US Food and Drug Administration to issue

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an advisory about risk of fractures in adults taking PPIs chronically.<sup>11</sup> In this context, a less conservative test assessing if the odds ratio was significantly greater than 1.0 (not just different from 1 in any direction) might have been more appropriate and may have yielded a statistically significant result.

These results suggest that GER/GERD does not play a major role in asthma pathogenesis and should thus strongly discourage the generalized use of PPIs for treatment of asthma. The tentative recommendation by the current National Heart, Lung, and Blood Institute guidelines<sup>12</sup> of an empirical trial of GERD therapy in patients with poorly controlled asthma (which was based on the few data available at the time the guidelines were written) is unjustified and should be promptly revised. Moreover, a recent review concluded that PPIs are not effective for reducing GERD symptoms in infants and are equally effective as other treatments in older children.<sup>13</sup> Given their potential adverse effects, these medications should thus be used with great restraint for treatment of GER/GERD during childhood. The substantial increase in use of PPIs in children during the last decade is worrisome and unwarranted.

The overuse of PPIs in childhood asthma and in pediatrics in general is another example of a subtle but frequent phenomenon in clinical practice: therapeutic creep. Clinicians extend the use of a treatment with real or suggestive therapeutic effects observed in a certain age group or in patients with a certain disease phenotype to other patients in whom the efficacy has never been demonstrated. Therapeutic creep in the treatment of asthma is not limited to PPIs. Combination therapy with inhaled corticosteroids and long-acting  $\beta$ -agonists has been shown to improve asthma symptoms and lung function in children whose symptoms are poorly controlled with inhaled corticosteroids,<sup>14</sup> but such a regimen is not superior to the use of monotherapy with inhaled corticosteroids in patients not previously treated with the latter.<sup>15</sup> This evidence notwithstanding, use of combination therapy has markedly drifted from children with severe disease, for whom it is justified, to children with milder disease, for whom it is not, and is currently prescribed as often as monotherapy for patients with mild asthma naive to inhaled corticosteroids.<sup>16</sup>

Therapeutic creep increases the risk of potential adverse effects without any added advantage for patients. It is also plausible to surmise that this phenomenon has substantially contributed to the marked increase in asthma drug costs, which are now the largest component of the direct costs for the disease.<sup>17</sup>

In conclusion, the study by Holbrook et al in this issue of *JAMA* indicates that chronic use of PPIs does not improve symptom control in children with asthma. Moreover, the observation that such use might be associated with serious adverse effects should suggest great caution in prescribing PPIs in general pediatric practice.

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