

Treatment of Pediatric Asthma with Proton Pump Inhibitors: Three Strikes, Game Over

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Empiric use of proton pump inhibitors (PPI) for the treatment of poorly controlled asthma has increased substantially in the past decade under the presumption that gastroesophageal reflux is precipitating symptoms. No PPI has a Food and Drug Administration (FDA) approved indication for the treatment of asthma symptoms. Use has been driven by data indicating that up to 80% of children and adults with asthma have reflux by pH probe monitoring and that nearly half of patients lack typical reflux symptoms. Data from controlled studies of adults have shown only a minimal improvement in peak expiratory flow with PPI use in the overall population, with only a slightly larger improvement in patients with diagnosed gastroesophageal reflux disease, and no effect on asthma exacerbation rate in one study. The single largest placebo-controlled study in children with poorly controlled asthma without gastroesophageal reflux symptoms found no improvement in any indices of asthma control, even in children with gastroesophageal reflux by pH probe test. In children, there is a disturbing increased risk for respiratory tract infections and potentially for activity related fractures with PPI treatment. These effects are consistent with known adverse effects of PPIs. Thus use of PPI should be confined to children with asthma who also have overt symptoms of gastroesophageal reflux. PPI are unlikely to improve poorly controlled asthma.

GASTROESOPHAGEAL REFLUX (GER) is the passage of gastric contents into the esophagus and is a normal process occurring multiple times daily. However, when it becomes symptomatic or results in additional complications, it is considered gastroesophageal reflux disease (GERD).¹ The National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma state that patients with asthma who have symptomatic GER should receive medical treatment for GERD.² There is no controversy with this strategy. On the other hand, the guidelines are silent about specifically recommending treatment for GER in patients with poorly controlled asthma despite optimal asthma therapy, and merely state that evaluation for GER should be considered even if typical GER symptoms are absent.² Herein lays the controversy.

Associations between asthma symptoms and gastric issues were noted more than 100 years ago by William Osler.³ A commonly accepted mechanism for asthma symptoms is bronchoconstriction induced by aspiration of acidic stomach contents into the airway, but even distal esophageal irritation initiates the esophageal-bronchial reflex to cause pulmonary symptoms.^{3,4} Acid may also indirectly induce vagal mediated effects on the upper airway or esophagus.^{3,4} Having

asthma or rhinosinusitis may predispose the patient to GER symptoms through mechanisms altering normal intra- and extra-thoracic pressure gradients.³ In addition, the physiological interrelationships between asthma, obesity, and obstructive sleep apnea may also contribute.^{3,5}

GER is conventionally diagnosed using ambulatory 24-hour esophageal pH monitoring when the distal esophageal pH is <4 for at least 5–7% of the study time.^{1,6,7} Other characteristics important in the diagnosis include the proximal reach and volume of reflux into the esophagus, which may be relevant to the development of asthma symptoms.⁶ As such, dual-probe esophageal pH monitoring (distal and proximal) in patients with asthma may better associate GER with symptoms such as nocturnal cough.^{6,8}

The overall prevalence of GER in Western countries is 10% to 20% of the population,⁹ but it is present in up to 80% of children and adults with asthma by ambulatory pH probe monitoring.^{10,11} However, nearly half of these patients (40%) have no symptoms (silent GER).^{5,12} The assumption that poorly controlled asthma is due to silent GER has generalized the use of the proton pump inhibitor (PPI) outside the population for which it was approved by the Food and Drug Administration (FDA) and into mainstream therapy for both pediatric and adult patients with asthma. PPI use has soared

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in recent years. Nexium[®] (esomeprazole) has been the second most prescribed drug since 2008,^{13–15} not including nonprescription purchases. More than 75% of patients on long-term PPI treatment have no verified indication for use.¹⁶ This phenomenon has been aptly dubbed “therapeutic creep,” which is the use of a treatment, which has proven efficacy in one population, in another population for whom efficacy has not been proven.¹⁷ Strike One: PPI use for the treatment of asthma symptoms is subject to therapeutic creep.

Omeprazole was the first PPI to be approved by the FDA in 1989, and the first randomized placebo-controlled trial in asthma was published only 5 years later.¹⁸ A meta-analysis published in 2010 identified nine randomized placebo-controlled trials of PPI therapy in adult patients with asthma, and included the most recent and largest trial of nearly 1,000 patients.^{19,20} Morning peak expiratory flow (PEF) was the primary endpoint selected for comparison in the meta-analysis because of its relationship to airway hyperresponsiveness.^{19,21} The meta-analysis demonstrated a small but statistically significant improvement in PEF (8.68 L/min) in participants who received PPI therapy. However, this change is clinically unimportant, as increases of 20 L/min to 25 L/min in PEF from baseline are considered the minimal patient perceivable improvement.^{21,22} None of the three largest trials (two of which had a treatment period of 6 months) demonstrated a statistically significant improvement in PEF.¹⁹ Seven of the trials required GERD diagnosis for inclusion, and in this population PEF improved by 17 L/min, which approaches the minimally important improvement criteria. Importantly, only one large trial used episodes of poor asthma control rather than PEF as the primary outcome, which is a more clinically relevant measure.^{5,19} In this trial of adults with poorly controlled asthma but without symptomatic GER or a prior diagnosis of GERD, there was no difference in episodes of poor asthma control between patients treated with esomeprazole or placebo for 6 months.⁵ These data from the trials strongly indicate that there is little or no role for PPI use as adjunctive therapy for asthma in adults.

The majority of studies conducted in pediatric patients with asthma have been of small sample size, not blinded, uncontrolled, or which have used a combination of anti-reflux treatments, making it difficult to determine the efficacy of PPI therapy.²³ In two studies of school-aged children with moderate or severe persistent asthma and a diagnosis of GERD, treatment with esomeprazole or lansoprazole plus other anti-reflux drugs in a nonrandomized open-label trial resulted in a reduction in asthma medication use and exacerbations compared to treatment in children who had a normal pH probe test.^{24,25} In another study, 11 of 14 children with moderate persistent asthma treated clinically for diagnosed GERD with a PPI for at least a year and who demonstrated improvement in asthma symptoms had an increase in asthma exacerbations when switched to ranitidine.²⁶ In 29 children with endoscopically proven GERD and difficult to treat severe asthma, 12 weeks treatment with PPI improved scores on the Childhood Asthma Control Test²⁷ but not FEV1 nor PEF variability, and similar numbers of children required step-up or had a step-down of asthma therapy.²⁸ In the first placebo-controlled trial of a PPI in a small number children with intermittent or mild to moderate persistent asthma and symptoms and a diagnosis of GERD ($n=38$), there was no

difference between groups for pulmonary function, rescue inhaler use, or quality of life.²⁹ In the largest trial ($n=306$) conducted by the American Lung Association Asthma Clinical Research Centers network, children with poorly controlled asthma despite treatment with fluticasone propionate $\geq 176 \mu\text{g/day}$ without symptoms of GER requiring treatment were randomized to lansoprazole or placebo for 6 months.¹² There were no differences between treatments for any asthma outcomes including the childhood Asthma Control Questionnaire,³⁰ episodes of poor asthma control, asthma-related quality of life, pulmonary function, or bronchial hyperresponsiveness. In the 115 children with an adequate 24-hour esophageal pH monitoring test at baseline, there was also no difference between treatments and there were no differences in gastrointestinal symptoms between children with a positive pH probe test compared to those with a negative test. Thus this study conclusively demonstrated the lack of beneficial effect of PPI therapy for the treatment of asthma symptoms in children with poorly controlled asthma. Strike Two: PPI therapy is not efficacious in reducing asthma symptoms.

Of concern, the Asthma Clinical Research Centers network trial¹² noted an increase in adverse effects in the children treated with lansoprazole compared with placebo. In children treated with lansoprazole, there were statistically significantly more reports of upper respiratory tract infection, sore throat, and bronchitis (though not pneumonia) compared to placebo.¹² PPI use may increase the risk of respiratory infections by decreasing gastric pH and enabling bacterial colonization of the stomach.^{31,32} In a recent meta-analysis, four of five case-controlled studies clearly found an increased odds ratio (1.16 to 1.73) for community-acquired pneumonia among PPI users.³³ In a prospective observational study of young children (aged 4 to 36 months) with GERD treated with PPI or ranitidine for least 2 months, the odds ratio for pneumonia was 6.39.³⁴ At this time, no PPIs carry a warning in the FDA-approved product label for risk of pneumonia.

Although not a statistically significant finding, results from the Asthma Clinical Research Centers network trial¹² also noted an increase in activity-related bone fractures in children treated with PPI compared with placebo ($p=0.06$). Had there been one additional fracture in the PPI-treated children, the finding would have reached statistical significance. Hip, wrist, and spine fractures are a well-established adverse effect of long-term PPI use, and the FDA requires warning labels for all available PPI products.^{35,36} In two meta-analyses, PPI use of <1 year was also associated with an increased odds ratio of 1.25 to 1.39 for fracture.^{35,36} Purported mechanisms for increased fracture risk are altered calcium absorption or inhibition of osteoclastic bone resorption.^{35–37}

Although not yet identified as safety concerns for children, additional adverse effects associated with PPIs, which are clinically important enough to be included as warnings in the drug label, are an increased risk of *Clostridium difficile* infection, magnesium deficiency, harmful drug interactions, vitamin B12 deficiency, and acute interstitial nephritis. Strike Three: PPI use for the treatment of asthma symptoms in children is associated with an increased risk of adverse effects.

There has been an alarming increase in the use of PPIs in the past decade, with a doubling of the number of children exposed from 2000 to 2005.^{12,38} With the loss of patent

protection, more PPIs will become available without a prescription, potentially increasing the number of children treated without physician or pharmacist involvement in the decision. Thus the incidence of adverse effects from PPIs will surely increase in the pediatric population. It is without controversy that PPIs are appropriate treatment for symptoms associated with GER in children with or without asthma.¹ But there is no evidence to support PPI treatment for uncontrolled asthma symptoms in children who do not also have symptomatic GER, Game Over.

Author Disclosure Statement

No conflicting financial interests exist.

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