*AFP* Journal Club

*The Story Behind the Study*

# PPIs, Childhood Asthma, and the Problem of Therapeutic Creep

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**Purpose**

In *AFP* Journal Club, three presenters review an interesting journal article in a conversational manner. These articles involve "hot topics" that affect family physicians or "bust" commonly held medical myths. The presenters offer opinions about the clinical value of the individual study discussed. The opinions reflect the views of the presenters, not those of *AFP* or the AAFP.

**Article**

Holbrook JT, Wise RA, Gold BD, et al.; Writing Committee for the American Lung Association Asthma Clinical Research Centers. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *JAMA*. 2012;307(4):373-381.

For more information on evidence-based medicine (EBM) terms, see the EBM Toolkit at http://www.aafp.org/afp/ebmtoolkit.

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## Do PPIs improve symptoms in children with poorly controlled asthma?

*Bob:* Previous studies have left open the question of whether proton pump inhibitors (PPIs) improve asthma symptoms. There may be benefit to PPI use in adults with asthma and reflux symptoms. However, there is no benefit in those without reflux symptoms. It has been hypothesized that untreated gastroesophageal reflux is sometimes responsible for inadequate asthma control in children. With 2.6 million PPI prescriptions written for children in 2009 and a growing body of evidence regarding their adverse effects, it is important to determine if PPIs improve asthma control in this population.[1]

## What does this article say?

*Bob:* The double-blind, randomized study enrolled 306 children six to 17 years of age with poorly controlled asthma. Inclusion criteria were: use of short-acting beta agonists two or more times per week; nocturnal awakenings with asthma symptoms more than once a week during the month before enrollment; two or more emergency department visits, unscheduled physician visits, courses of prednisone, or hospitalizations for asthma in the previous year; or an Asthma Control Questionnaire (ACQ) score of 1.25 or more at the screening visit.

Those children who met the inclusion criteria were randomized to lansoprazole (Prevacid) or placebo daily for 24 weeks and were assessed every four weeks. The primary outcome was change in ACQ score, which uses a combination of subjective indicators (e.g., cough, nocturnal symptoms, activity level) and objective measures (e.g., bronchodilator use, pulmonary function testing). Scores range from 0 to 6, with a score less than 0.75 suggesting well-controlled asthma and a score greater than 1.5 suggesting poorly controlled asthma.

The study showed that symptoms did not improve in children taking lansoprazole compared with those taking placebo at any point in the 24 weeks of follow-up. A subgroup of patients (n = 115) underwent 24-hour esophageal pH monitoring, and lansoprazole did not improve asthma symptoms even in those with documented gastroesophageal reflux (43% of patients).

## Should we believe this study?

*Mark:* This is a very well-done study. The blinding and randomization processes are well documented, a prestudy sample size was calculated to draw robust statistical conclusions, and follow-up was excellent (88% of the participants completed the 24-week study, and 94% of monthly follow-up visits were attended). The two groups also appeared well matched, particularly regarding disease ▶

severity, which was equal between the two groups at baseline (ACQ score of 1.6). At 24 weeks, the ACQ score decreased by 0.1 point in the PPI group and by 0.2 points in the placebo group (not a clinically significant difference). Adverse events in both groups were also recorded.

*Jill:* Not only were there no benefits to PPI use, the adverse effects were striking. Children in the PPI group had statistically more upper respiratory tract infections, sore throats, and bronchitis. Perhaps an even greater concern is six children taking lansoprazole developed fractures compared with only one taking placebo. Because these numbers are small, this sixfold increase is not statistically significant, and I wonder if significant demineralization could really occur in six months. Although there may be other explanations (such as prior steroid use), this finding is consistent with previous studies linking PPI use with increased fracture risk[2,3] and is worth noting.

*Bob:* An association does not imply cause and effect. However, when multiple criteria are met (e.g., strength of the association, consistency, specificity, temporality, dose-response relationship, biologic plausibility, coherence, experimental evidence, analogy), the likelihood of a causal relationship increases. In this case, the association between risk of fracture and PPI use has been demonstrated consistently, is a temporal relationship, and has a scientifically plausible reason (i.e., lack of an acidic environment decreases calcium absorption).

*Mark:* And, fractures are not the only deleterious effect linked to PPIs. Others include *Clostridium difficile* colitis,[4-6] community- and hospital-acquired pneumonia,[7,8] hypomagnesemia,[9,10] and drug-drug interactions, including malabsorption of certain drugs or supplements.[11]

*Jill:* Despite these potential adverse events, more and more children are being prescribed PPIs. In the first six years after a liquid preparation became available for children, PPI use skyrocketed 16-fold.[12] Many of these PPI prescriptions were written for so-called gastroesophageal reflux disease in infants. Somehow we have forgotten that 40% to 70% of infants spit up daily because of an anatomically short esophagus, a noncompliant stomach, and feeding volumes that are proportionally much greater than older children and adults.[13] Yet, spitting up and colic are all too often inexplicably attributed to gastroesophageal reflux disease, resulting in a prescription for a PPI—a treatment with no proven benefit and the potential for harm.

*Bob:* The use of a therapy in patients one would intuitively think (or hope) might benefit, but in whom no benefit has been documented, has been termed therapeutic creep.[14] The use of PPIs for poorly controlled asthma is an example of this phenomenon, and Jill noted the use of PPIs in infants who spit up and have colic.

*Mark:* Other examples of therapeutic creep are using combination long-acting beta agonist/corticosteroid therapy (e.g., Advair) for poorly controlled asthma before an adequate trial of corticosteroid monotherapy; and using cyclooxygenase-2 inhibitors for musculoskeletal pain in patients without peptic ulcer disease. Prescribing Vioxx for every ache and pain should have taught us a lesson.

## What should the family physician do?

*Bob:* In 2009, PPIs accounted for $13.9 billion in sales worldwide.[15] However, three studies have demonstrated that 69% of all PPI prescriptions are for patients without an appropriate indication.[16-18]

*Mark:* Family physicians should remember the appropriate indications for PPI use, and the deleterious effects attributed to these drugs.

*Jill:* Also, we need to keep an eye out for therapeutic creep—it's likely more prevalent in our daily practice than we think.

### Main Points

- PPIs provide no benefit and are associated with increased harms in children with poorly controlled asthma.
- Therapeutic creep is an all-too-common phenomenon that clinicians need to recognize and avoid.

### EBM Points

- An association does not confer causation. However, when multiple criteria are met (e.g., strength of the association, consistency, specificity, temporality, dose-response relationship, biologic plausibility, coherence, experimental evidence, analogy), the likelihood of a causal relationship increases.

If you conduct a journal club and want to know the next article that will be discussed, or if you would like to suggest an article for discussion, e-mail afpjournal@aafp.org.

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