

## Infants and Proton Pump Inhibitors: Tribulations, No Trials

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In this issue of the *Journal*, Barron et al (1) report their retrospective analysis of data from 4 US health plans, in which they document an enormous rise in the use of proton pump inhibitors (PPIs) in infants for presumed gastroesophageal reflux disease (GERD): In the 4 years from 2000 through 2003 there was at least a 4-fold increase, and in the 6 years from 1999 through 2004, there was a >7-fold increase. One of the PPIs, available in a child-friendly liquid formulation, saw a 16-fold increase in use during that 6-year period.

Overall, about 0.5% of the roughly 1 million infants in the study database received one of these drugs during their first year of life. Nearly 50% of the infants started taking a PPI before 4 months of age, and the median duration of treatment was 6 to 8 weeks with an isolated "gastroesophageal reflux" code, but about 3 months if comorbidities were also present. These are not clearly identified, but we presume from the tables Barron et al provide that they include other codes, such as those for respiratory conditions or "allergic diagnoses." General pediatricians provided somewhat more than half of the prescriptions, with pediatric gastroenterologists writing most of the rest. Fewer than 10% of the infants had any diagnostic testing, and for one third of the infants the PPI was the first-line therapy.

Barron et al point out that their study did not evaluate the clinical effectiveness of PPI treatment, and that it is possible that that PPI use did not improve symptoms in these infants. However, they also attempt to justify the high prevalence of PPI use in infants. For example, they state: "The diagnosis of upper respiratory conditions in 23% of the cohort is not surprising. It has been documented in

several clinical trials that infants with untreated GERD are at greater risk for the development of asthma, recurrent pneumonia, and recurrent bronchitis." To support this statement, they cite 4 references. Two are in local journals from India and China (2,3) and one is in a tropical medicine journal (4); none is a clinical trial. They are reports of particularly poor quality that do not support their assertion that GERD in infants is a cause of respiratory disease. The one careful, controlled study (5) did not include infants but older children, who were not shown to have GERD in the first place and were of an age group in which respiratory symptoms of an infectious etiology are prevalent.

Elsewhere the authors state: "The 'typical' course of PPI lasted 1 to 3 months, with mean age at index of 4 to 5 months and mean age at discontinuation of 7 to 8 months. This pattern of therapy was consistent with what has been shown in a recent survey of pediatric gastroenterologists' PPI usage patterns (6)." The cited abstract, describing a survey done in 1999, did not report on patterns of PPI therapy in infants, however. In addition to blurring distinctions between data from infants and children in their discussion, Barron et al also blur distinctions between physiological gastroesophageal reflux and GERD (7), thus largely invalidating their rationalization for the appropriateness of the highly prevalent use of PPIs in infants.

*So, what are we treating with PPIs in all of these infants?* We could be treating any of the symptoms with which infants may manifest reflux: regurgitation, signs of pain presumed to be esophageal (crying, arching, feeding refusal), failure-to-thrive (which may be due to either regurgitation or feeding refusal), or any of the upper or lower respiratory manifestations with which GERD may present in infants. As far as one can tell from coding details in the study by Barron et al (1), "excessive crying" was specifically coded in 2%, "colic" in 20%, "problems feeding" in 23%, and "failure-to-thrive" in 5% of the total cohort. The nonspecific codes of "gastroesophageal reflux" (59%) and "esophagitis" (21%) were used for most of the infants, although the latter was clearly a presumptive diagnosis because fewer than 10% had undergone any of the diagnostic testing that could have

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documented esophagitis, and gastroesophageal reflux is a physiological, self-limited occurrence in most otherwise healthy infants. In terms of respiratory manifestations, a full 23% were coded with "upper respiratory infection" and 9% were coded with "bronchitis or bronchiolitis." "Allergic diagnoses" were coded in 10%. It is unlikely that all of these codes were meant to warrant the PPI therapy, this ambiguity being one of the limitations of the retrospective use of coding details. Multiple overlapping codes were present in at least some of the infants.

In addition to treating symptoms, PPI use could also be directed at treating endoscopic erosions or histological esophagitis, although there is limited evidence of this in the article. Furthermore, even in subspecialty pediatric gastroenterology practice, such erosive disease is uncommon in infants, except in those with underlying disorders such as neurological disease or repaired esophageal atresia. Intraesophageal pH monitoring is another potential outcome variable that PPI use would undoubtedly improve, but intraesophageal pH is only a surrogate for possible abnormality, based on its association with esophagitis or with symptoms; pH probe results are not in and of themselves adequate goals of therapy. Less acid in the esophagus is expected on an acid suppressant; this does not confirm that the acid suppression and symptoms are causally related.

*What robust evidence supports this huge increase in the use of PPIs in infants?* Of the few double-blind, randomized placebo-controlled trials (DBRPCTs) of PPI efficacy for symptom relief in infants, none shows benefit. For example, a DBRPCT of omeprazole in infants by Moore et al (8), using the outcome variable of irritability in a 2-week/2-week crossover design, showed similar improvement in irritability in infants while taking placebo and while taking omeprazole, despite documented reduction of esophageal acidification in the omeprazole group. Another DBRPCT of omeprazole in premature infants showed a similar reduction in gastric acidity, but a lack of improvement in symptoms in either group, in a 1-week/1-week crossover design (9). It is possible that details of therapy, including short duration or low dose, may have obscured symptom efficacy in these 2 clinical trials. However, the natural history of developmental improvement in reflux symptoms during the first year of life (10), as illustrated by the Moore et al study, mandates a DBRPCT design for any efficacy study with symptoms as the outcome variable. The subjectivity and secondhand nature of the reporting of these symptoms also suggests the importance of using a validated instrument, including validation for responsiveness, to quantify these symptomatic outcomes (11,12).

*Are there other well-designed clinical trials of PPIs in progress?* The clinical trials registry at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifies only a handful of registered PPI trials in infants. Of those, only 4 are DBRPCTs for efficacy,

and 1 of the 4 is limited to neonates. Two of the remaining 3 DBRPCTs involve a withdrawal design, in which all of the patients are treated with drug, and only the subsequent withdrawal of drug is a DBRPCT. Such a design has previously demonstrated weaknesses for studies in infant GERD (13). This design is fatally flawed for studying the efficacy of PPIs, drugs for which abrupt withdrawal after administration in healthy individuals results in symptoms due to rebound acid hypersecretion (14–16).

*Can we not simply extrapolate from the beneficial effects of PPIs on symptoms and endoscopy shown in DBRPCTs in adults and on the evidence that they improve pH probe parameters in infants, including premature infants?* Probably not, except for the small minority of infants who have severe acid reflux (ie, producing erosive disease). In most infants with GERD, extrapolating from data in older children or adults is hazardous; in infants the symptoms of GERD are different, the natural history of the symptoms is spontaneous resolution in all but about 5%, the maturing developmental status affects the disease course, the historical chronicity in each patient is limited, and young infants are treated with the buffering of milk formula or breast milk every few hours throughout the day (17). It may be that volume, rather than acid, is the predominant factor underlying most of the symptoms of infant GERD; even the crying and irritability may be due to the relatively huge meals infants must ingest to triple their weight within 12 months. Proton pump inhibitors, tremendously effective in reducing acid reflux, may not be effective in reducing symptoms due to large volumes of neutral-pH meals. Furthermore, the symptoms may not be related to non-acid reflux. Many of these symptoms/signs could be due to nonreflux causes, such as milk protein allergy, constipation (18), or developmental issues such as difficulty changing state (19). To determine whether PPIs are an appropriate therapy for symptoms, infants require their own adequately powered, carefully performed DBRPCTs of adequate duration, using rigorously validated and clinically appropriate outcome measures.

*What about the concern that infants comprise a particularly vulnerable group, which needs special protections when research is contemplated?* This concern is codified in the US Federal Policy Regulation 45 CFR 46, subpart B, conferring additional protections upon neonates involved in research. It is worth considering, however, that every infant treated with a drug without DBRPCT-confirmed efficacy is participating in an experiment: an experiment where  $n = 1$ , with no institutional review board oversight, no informed consent, and no possibility that the results of the experiment can benefit any other infant. Perhaps the parents of these infants should be required to sign consent for such single-subject experiments, acknowledging their awareness of lack of efficacy data.

*How can we possibly recruit for clinical trials in which we propose to infants' parents that their babies may be treated with a placebo?* We should simply acknowledge that we do not know whether the drug is efficacious for the particular presenting complaint and that it is possible that the drug and placebo will have equal efficacy (patients with erosive esophagitis excluded), with the placebo possibly having greater safety.

The issue of safety is particularly relevant to these youngest, most vulnerable patients, in whom there are few safety data concerning PPIs. Preliminary data suggest that long-term use of PPIs in older children is safe (20,21), but few received PPI therapy in infancy. Furthermore, these older children had endoscopically proven esophagitis, many had failed other treatments, and a GERD-provoking underlying disease was present in 79%. In these patients, therefore, the risk-benefit balance strongly favored PPI therapy. However, neither their ages nor clinical circumstances can be extrapolated to the infants reported by Barron et al (1), most of whom were treated empirically. Caution is now prompted by recent reports suggesting potential adverse effects of chronic gastric acid suppression, including higher prevalences of necrotizing enterocolitis in infants; acute gastroenteritis or community-acquired pneumonia in children; *Clostridium difficile* infections; and, in older adults, hip fractures and vitamin B<sub>12</sub> deficiency (22-27). These data require corroboration and may be specific to certain ages, durations of treatment, or other qualifiers. They remind us that until good data convince us otherwise, there are potential downsides to seemingly benign treatments. Nutritional or infectious downsides may considerably compromise infants and are of greater concern when they may be due to treatment for symptoms of unclear etiology that may resolve spontaneously. In addition to their ability to demonstrate efficacy, DBRPCTs are also one of the most effective ways to distinguish common events, such as gastroenteritis or community-acquired pneumonia, that are adverse reactions to drugs from those that are not drug related (28,29).

The good news is that the number of infants being treated with these drugs, as documented in the article by Barron et al, indicates that there are enough infants to populate large, multicenter DBRPCTs. Such DBRPCTs could be designed collaboratively among industry, physician experts in infant GERD, and regulatory bodies, and carried out in multiple clinical centers committed to establishing a scientific basis for our management practices. Given the benefits accruing to industry from the pediatric market overall, and the potential for a 6-month extension of market exclusivity in the United States for a given drug, it seems reasonable that industry should underwrite these studies. Until such studies show efficacy, every prescription we write for acid suppressive treatment for these symptoms in infants is a prescription for an experiment. Infant patients are owed more than that.

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