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Efficacy of Proton-Pump Inhibitors in Children With Gastroesophageal Reflux Disease: A Systematic Review

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abstract

INTRODUCTION: Use of proton-pump inhibitors (PPIs) for the treatment of gastroesophageal reflux disease (GERD) in children has increased enormously. However, effectiveness and safety of PPIs for pediatric GERD are under debate.

OBJECTIVES: We performed a systematic review to determine effectiveness and safety of PPIs in children with GERD.

METHODS: We searched PubMed, Embase, and the Cochrane Database of Systematic Reviews for randomized controlled trials and crossover studies investigating efficacy and safety of PPIs in children aged 0 to 18 years with GERD for reduction in GERD symptoms, gastric pH, histologic aberrations, and reported adverse events.

RESULTS: Twelve studies were included with data from children aged 0–17 years. For infants, PPIs were more effective in 1 study (compared with hydrolyzed formula), not effective in 2 studies, and equally effective in 2 studies (compared with placebo) for the reduction of GERD symptoms. For children and adolescents, PPIs were equally effective (compared with alginates, ranitidine, or a different PPI dosage). For gastric acidity, in infants and children PPIs were more effective (compared with placebo, alginates, or ranitidine) in 4 studies. For reducing histologic aberrations, PPIs showed no difference (compared with ranitidine or alginates) in 3 studies. Six studies reported no differences in treatment-related adverse events (compared with placebo or a different PPI dosage).

CONCLUSIONS: PPIs are not effective in reducing GERD symptoms in infants. Placebo-controlled trials in older children are lacking. Although PPIs seem to be well tolerated during short-term use, evidence supporting the safety of PPIs is lacking. *Pediatrics* 2011;127:925–935

Gastroesophageal reflux (GER) is characterized by the passive movement of gastric contents into the esophagus. Physiologically, GER occurs several times daily in healthy infants, children, and adults.[1–3] Gastroesophageal reflux disease (GERD) in infants and children is described as GER that causes troublesome symptoms and/or complications.[4,5] On the basis of a large claim database that uses *International Classification of Diseases, Ninth Revision* (ICD-9) codes, GERD was diagnosed in 12.3% of North American infants and in 1% of other pediatric age groups.[6] Symptoms of GERD are often nonspecific and may vary widely from regurgitation to excessive crying and respiratory symptoms. GER has the potential to cause severe complications such as esophagitis and failure to thrive. GERD can also have a major effect on the daily life of caregivers and on health care costs, which have been estimated to be US $2386 per patient per 6 months.[7] Although taking medical history and performing a physical examination will often suffice, pH monitoring, occasionally combined with intraluminal impedance monitoring (pH-MII) and/or endoscopy, can be conducted if necessary. pH-MII is able to detect non–acidic reflux events as well and is of additional value in infants because of feed-buffering.[8,9]

For mild infant GERD, parental guidance and education combined with feed thickeners and/or positioning therapy will often suffice. Also, in older children and adolescents, dietary and behavioral changes frequently reduce symptoms significantly.[10–12] However, when pharmacologic treatment is indicated, antisecretory agents play a key role, and proton-pump inhibitors (PPIs) are on the front row. In recently published guidelines, conducted by the European Society for Pediatric Gastroenterology Hepatology and Nutrition and the North American Society for Pe-

diatric Gastroenterology Hepatology and Nutrition in 2009, regarding pediatric GER, empiric, antisecretory treatment for infants with crying and distressed behavior may be considered, although clinical recovery may be ascribed to a placebo reaction or physiologic symptom resolution with time.[4] In children and adolescents with heartburn, the use of acid-suppressing agents is also recommended; however, the supporting data were extrapolated from adult studies.[4] Current guidelines lack a systematic review (SR) of the available evidence. Therefore, it remains unclear whether some recommendations are based on an expert opinion of the guideline committee or on scientific evidence. A recently published SR did not include recent randomized controlled trials (RCTs) and excluded adolescents with GERD.[13]

PPIs (omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole) inhibit gastric acid secretion by selectively blocking the gastric parietal cell H^+K^+ ATPase (also called the proton pump), an enzyme that is involved in the last step of acid secretion in gastric parietal cells. Although the effectiveness of PPIs in children is under debate, PPI use in infants and children with GERD has increased enormously during the last decade.[14–16] PPIs are generally well tolerated[17] but have some shortcomings and may increase susceptibility to acute gastroenteritis and community-acquired pneumonia,[18,19] respiratory infections,[13] gastric polyps,[20] and bacterial overgrowth.[13]

Although PPIs are widely considered the most effective acid-suppressive therapy for adults with GERD,[21,22] the effectiveness and safety of PPIs in infants and children with GERD is less clear. Therefore, the aim of this study was to systematically review the current literature to investigate and summarize the quantity and quality of the

evidence for the efficacy and safety of PPIs in infants, children, and adolescents with GERD.

METHODS

Search Strategy

We searched Medline, Embase, the Cochrane Database of Systematic Reviews electronic database, and the Cochrane Controlled Trials Register for SRs, RCTs, and crossover studies from inception to May 2010. The key words used to describe the study population were "proton-pump inhibitors" (Medical Subject Headings [MESH] and all fields), "gastroesophageal reflux" (MESH and all fields), "gastroesophageal symptoms," "extraesophageal symptoms," "GERD," "esophagitis" (MESH and all fields), "infant" (MESH and all fields), "child" (MESH and all fields), and "adolescent" (MESH and all fields). No language restriction was applied. Reference lists of reviews and included studies were searched by hand to identify additional studies. The full search strategy is available from the corresponding author.

Study Selection

Two reviewers (Dr van der Pol and Ms Smits) independently screened all abstracts of identified SRs for eligibility. Inclusion criteria were: (1) the study was an SR, RCT, or crossover study; (2) the study population consisted of children aged 0 to 18 years with GERD and/or esophagitis; (3) one of the aims of the study was to evaluate the efficacy, adverse effects, tolerability, safety, and/or cost-effectiveness of PPI therapy or patient satisfaction, decrease in GERD symptom score, or change in number of acid reflux episodes and/or reflux index with PPI use; (4) the intervention consisted of PPIs and was compared with placebo, no treatment, or alternative treatment; and (5) the outcome measure was "treatment success" as determined

by the authors of the studies. Studies with asthmatic patients, mentally retarded children, children with cystic fibrosis, children with eosinophilic esophagitis, children who had undergone surgical therapy, or children who had had previous use of any other therapy besides PPIs (such as histamine H_2 receptor antagonist, antacids, and/or prokinetics) were excluded.

All potentially relevant studies and the studies for which the abstracts did not provide sufficient information for inclusion or exclusion were retrieved as full articles.

Quality Assessment

The full texts of included reviews were validated by 2 assessors (Ms Smits and Dr van der Pol) independently by means of a standardized list to validate SRs. Because a valid SR was not encountered, 2 reviewers (Ms Smits and Dr van der Pol) rated the methodologic quality of all identified studies by using the Delphi list (Table 1), a standardized list for RCTs.[23] Methodologic quality scores were calculated as a percentage of the maximum quality score on the Delphi list. High quality is defined as a score of ≥60% (ie, ≥6 points), and low quality is defined as a score of <60%. If disagreement between the 2 reviewers existed, consensus was formed, when possible, or a third reviewer (Dr Tabbers) made the final judgment.

Data Extraction

Structured data extraction was performed from the original reports by 2 reviewers (Ms Smits and Dr van der Pol) independently. Data derived from included articles contained items such as author and year of enrollment, study setting, methods, type of participants, method of GERD assessment, type of intervention, follow-up, outcome measures, and results. If disagreement between the 2 review-

TABLE 1 The Delphi list

Study Population	Blinding	Analysis
Was a method of randomization performed?	Was the outcome assessor blinded?	Were point estimates and measures of variability presented for the primary outcome measures?
Was the allocation of treatment concealed?	Was the care provider blinded?	Did the analysis include an intention-to-treat analysis?
Were the groups similar at baseline regarding the most important prognostic indicators (age, gender, disease duration, disease severity)?	Was the patient blinded?	Was the withdrawal/drop-out rate at <20% and equally distributed?
Where both inclusion and exclusion criteria specified?		

ers existed, consensus was formed, when possible, or a third reviewer (Dr Tabbers) made the final judgment.

RESULTS

The search strategy generated 814 titles and abstracts (see Fig 1), of which only 15 studies met our inclusion criteria. After retrieving the full-text articles, 3 articles were excluded because of the lack of a control group or different outcome measures[24–26] (Fig 1). Of the included studies, 10 were RCTs and 2 were crossover trials. Data from 895 participants (0-17 years old) were included. Studies were conducted in Europe, Australia, and North America. One study was performed in a tertiary hospital on preterm infants with symptoms suggestive of GERD[27]; the other trials were outpatient studies, of which 9 were performed in a general pediatric department, 2 in a pediatric gastroenterology department.[28,29] Quality scores and study characteristics of the included studies[27–38] are listed in Table 2.

The reviewers initially agreed on 85.8% of the quality items. Prevalent shortcomings of the included studies consisted of missing point estimates and measures of variability presented for the primary outcome measure ($n = 8$), no intention-to-treat analysis ($n = 5$), and no blinding of the outcome assessor ($n = 5$). The mean score for overall methodologic quality was 7.6. Because

of the heterogeneity between the included studies with regard to the participants, interventions, and outcome measures, a meta-analysis was not possible. Therefore, all studies are discussed separately. Included studies were subdivided on the basis of the age of the investigated population (infants, children, and adolescents) because of the different presentations of GERD symptoms in these groups and, herewith, the possible difference in efficacy.

If safety was an outcome measure in the included studies, it was monitored by the reported adverse events (AEs). Of the reported AEs, a selection was made of treatment-related adverse events (TRAE) that were judged by the clinicians treating the subject or the authors of the conducted study. The results are presented in this way in the hereafter-described subgroups.

Infants

We identified 5 placebo-controlled studies for which the authors described the efficacy and/or safety of PPIs (lansoprazole,[29,30] omeprazole,[27,28] and pantoprazole[31]) in infants (34 weeks' postmenstrual age to 12 months) with GERD. The mean score of the methodologic quality was 7.8. Alterations of GERD were monitored by differences in symptoms such as crying/irritability and spilling,[27,28,30] in questionnaire outcomes (I-GERQ-MH
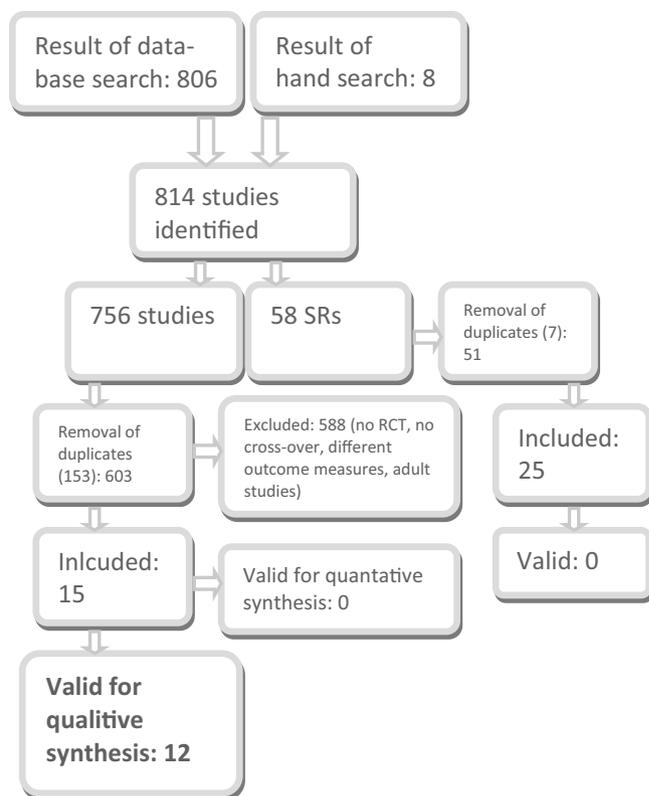
FIGURE 1
Search strategy.

[Infant Gastroesophageal Reflux Questionnaire Medical History],[30] GSQ-I [GERD Symptom Questionnaire Infants],[31] I-GERQ-R [Infant Gastroesophageal Reflux Questionnaire Revised][29]), and/or in pH monitoring.[27,28]

PPIs compared with a placebo were not effective in reducing GERD symptoms in the 2 studies that used omeprazole.[27,28] Compared with placebo, lanzoprazole and pantoprazole were equally effective in 2 studies[30,31] for reducing GERD symptoms. In a study that used lansoprazole, PPIs were more effective compared with hydrolyzed formula.[29] One of the 5 studies did reveal a significant decrease in irritability over time in the PPI and placebo groups.[28] Omeprazole was more effective compared with placebo in reducing gastric acidity, as shown by pH-monitoring results.[27,28]

The authors of 3 studies reported AEs[27,30,31]: 1 study found no AEs,[27] 1 study found mild-to-moderate AEs,[31] and 1 study found a significant difference in the frequency of serious AEs (lower respiratory tract infection in the PPI group).[30] In the case of the latter study, the AE was judged not to be related to treatment by the clinicians who were treating the subjects. No significant differences were detected between the studied groups in reported TRAEs.[30,31]

Children

We retrieved 5 studies that reported on the effect of esomeprazole,[33] lansoprazole,[35] omeprazole,[34,36] and pantoprazole[32] in children with GERD (aged 6 months to 13.4 years). The methodologic quality of these studies had a mean score of 6.8. Efficacy was assessed by changes in GERD symptoms,[33–36] questionnaire responses (Gastroesophageal Reflux Assessment of Symptoms in Pediatrics Question-

naire[32]), and/or pH monitoring[35,36] and/or endoscopy.[34–36] Of these RCTs, 2 were dose-finding studies that used 2 PPI doses[32,33]; the other studies compared PPIs by using other antireflux therapies as controls (ranitidine[34,36] and alginates[35]).

All studies revealed that PPIs were equally effective compared with what was given in the control groups in reducing GERD symptoms. When comparing the different groups to baseline, GERD symptoms were significantly reduced in all groups.

The authors of 2 studies[35,36] reported gastric pH findings and found that PPIs were more effective at reducing gastric acidity than alginate or ranitidine, but the reduction of macroscopic and histologic scores during endoscopy were similar in all study groups (PPI versus ranitidine or alginate) compared with baseline.[34–36]

Mild-to-moderate AEs were described in 2 study reports.[32,33] The most common reported TRAEs included headache ($n = 6$) and diarrhea ($n = 3$).[32,33]

Adolescents

We included 2 studies that reported on the efficacy of esomeprazole[38] and pantoprazole[37] in adolescents (12–17 years) with GERD. The mean score of the methodologic quality was 8.8. Efficacy of the PPIs was assessed by symptom assessments[38] or questionnaires (Gastroesophageal Reflux Assessment of Symptoms in Pediatrics Questionnaire).[37]

Both studies revealed that PPIs were equally effective in reducing GERD symptoms compared with what was given in the control groups. Because both of them were dose-finding studies, control groups received PPIs but in different quantities. When comparing the different groups to baseline, GERD symptoms were significantly reduced in both groups.

TABLE 2 Study characteristics

Study and Quality	Setting, Participants, Diagnosis	Intervention (No. of Participants, Age, Mean ± SD)	Control Intervention (No. of Participants, Age, Mean ± SD)	Follow-up	Outcome Measures and Results
Infants					
Moore et al[28] (2003), high quality (9)	Pediatric gastroenterology clinic; irritable/crying/spilling infants (3–12 mo old) with a reflux index of >5% on pH monitoring and/or abnormal esophageal endoscopy/histology	Omeprazole: <10 kg, 10 mg/d, or >10 kg, 2 × 10 mg/d; placebo (n = 15, NS per group, 5.1 ± 2.0 mo)	Placebo, omeprazole (n = 15, NS per group, 5.1 ± 2.1 mo)	4 wk (LFU: 4 of 34 [6%])	Reduction in reflux index: omeprazole, −8.9 ± 5.6; placebo, −1.9 ± 20 (P < .001); change in cry/fuss score: omeprazole, 191 ± 120; placebo, 201 ± 100 (P = 4); change in visual analog score of infant irritability: omeprazole, 5.0 ± 3.1; placebo, 5.9 ± 2.1 (P = .214); baseline vs period 2 (placebo and omeprazole): baseline, 6.8 ± 1.6; period 2, 4.8 ± 2.9 (P = .008)
Orenstein et al[30] (2009), high quality (9.5)	General pediatric clinic; infants (4–51 wk old) with symptomatic GERD, 3 times I-GERQ-MH screening (score not stated); crying/fussing/ irritability 1 h after <25% of feeds; no response to conservative therapy	Double-blind period: lansoprazole: ≦10 wk, 0.2–0.3 mg/kg per d, or >10 wk, 1.0–1.5 mg/kg per d; open-label period: lansoprazole (n = 81, 4–49 wk, mean: NS)	Double-blind period: placebo; open-label period: lansoprazole (n = 81, 4–51 wk, mean: NS)	Before treatment: 1–2 wk; double-blind: 1–4 wk; open-label: 2–4 wk; after treatment: 30 d (LFU: 2 of 162 [1.2%])	Responder status: >50% reduction from baseline in feeding-related crying: lansoprazole, 54%; placebo, 54% (not significant); changes in GERD symptoms: lansoprazole, −20; placebo, −20 (not significant); improvement of GAS: lansoprazole, 56%; placebo, 51% (not significant); mild/moderate AEs: lansoprazole, 62%; placebo, 46% (P = .058); most frequent AE, upper respiratory tract infection: lansoprazole, 22%; placebo, 21%; serious AEs: lansoprazole, 12%; placebo, 2% (P = .032); most frequent AE, lower respiratory tract infection: lansoprazole, 12%; placebo, 2%; mild/moderate TRAEs: lansoprazole, 15%; placebo, 16% (not significant)
Winter et al[31] (2010), high quality (8)	General pediatric clinic; postterm infants (>28 d to <12 mo old) and preterm infants (corrected age: 44 wk to <12 mo old) with GSQ-I score > 16; clinical diagnosis of suspected, symptomatic, or endoscopy-confirmed GERD	Open-label period: pantoprazole: 1.2 mg/kg per d; double-blind period: pantoprazole (n = 52, 5.15 ± 2.81 mo)	Open-label period: pantoprazole; double-blind period: placebo (n = 54, 5.04 ± 2.81 mo)	Before treatment: 2–4 wk; open-label: 4 wk; double-blind: 4 wk (LFU: 0 of 106 [0%])	Withdrawal rate: pantoprazole, 6; placebo, 6 (not significant); change in weekly GERD symptom scores: pantoprazole, −2.39 ± 2.47 (P < .001); placebo, −2.52 ± 2.7 (P < .001); no significant changes between groups; mild/moderate AEs, upper respiratory infection most common, pantoprazole, 13%; placebo, 13% (not significant); TRAEs: NS
Omari et al[27] (2007), high quality (7)	General pediatric (inpatient) department; preterm infants (34–40 wk PMA) with reflux symptoms; reflux index of >5% on pH monitoring	Omeprazole: 0.7 mg/kg per d; placebo (n = 5, 34–40 wk PMA, 36.1 ± 0.7 wk)	Placebo; omeprazole (n = 5, 34–40 wk PMA, 36.1 ± 0.7 wk)	2 wk (LFU: not stated)	Change in gastric acidity: omeprazole, 13.9 ± 5.1; placebo, 53.8 ± 6.8 (P < .0005); esophageal acid exposure: omeprazole, 19.0 ± 4.5; placebo, 4.9 ± 3.4 (P < .01); acid GER episodes: omeprazole, 59.6 ± 26.7; placebo, 119.4 ± 20.9 (P < .05); change of GER symptom-assessment charts, symptom-assessment score: no significant changes; blood samples on days 6 and 13: blood chemistry or complete blood count (no significant alteration)
Khoshoo and Dhume[29] (2008), high quality (6)	Pediatric gastroenterology clinic; infants (3–7 mo old) with an I-GERQ-R score of ≥16 over a 1-wk period	Lansoprazole: 15 mg/d (Lan1) or 2 × 7.5 mg/d (Lan2) (n = 15, 4.80 ± 1.18 mo [Lan1]; n = 15, 4.30 ± 1.01 mo [Lan2])	HF (n = 15, 4.60 ± 0.99 mo)	2 wk (LFU: 0 of 45 [0%])	Improvement of >30% in I-GERQ-R scores: Lan1, before, 26.6 ± 2.8; after, 20.6 ± 4.2; Lan2, before, 26.9 ± 3.7; after, 20.0 ± 3.3; HF, before, 25.9 ± 3.3; after, 25.8 ± 3.2; HF vs Lan1 or Lan2, P < .05

TABLE 2 Continued

Study and Quality	Setting, Participants, Diagnosis	Intervention (No. of Participants, Age, Mean ± SD)	Control Intervention (No. of Participants, Age, Mean ± SD)	Follow-up	Outcome Measures and Results
Children					
Tolia et al[32] (2006), high quality (8.5)	General pediatric practice; children (5–11 y old); endoscopy-proven GERD with a CSS of >16 on the GASP-Q	Pantoprazole: 10 mg/d (n = 19, 8.50 ± 1.65 y)	Pantoprazole: 20 or 40 mg/d (n = 18, 8.2 ± 1.48 y [20 mg/d]; n = 16, 7.60 ± 1.89 y [40 mg/d])	Before: 2 wk treatment: 8 wk; after: 2 wk (LFU: 1 of 53 [2%])	Change in GASP-Q in mean CSS: 10 mg/d, 129.2 vs 28.1; 20 mg/d, 134.6 vs 32.7; 40 mg/d, 132.3 vs 42.9 (P < .001); ISS, all 3 doses: belly pain, difficulty swallowing, nausea, pain after eating (all P < .001); chest pain (P < .006); PGA: disease improvement in all 3 doses (P < .001); CSS, ISS, and PGA: differences in mean score between groups: not significant; AEs: NS; mild or moderate TRAEs, most common: 10 mg/d, headache (3); 20 mg/d: abdominal pain (1) and increased appetite (1); 40 mg/d, headache (1); differences between groups: not significant
Gilger et al[33] (2008), high quality (7.5)	General pediatric practice; children (1–11 y old) with endoscopy- or histology-confirmed reflux esophagitis	Esomeprazole: <20 kg, 5 mg/d, or >20 kg, 10 mg/d (n = 26, mean NS [5 mg/d]; n = 31, mean NS [10 mg/d])	Esomeprazole: <20 kg, 10 mg/d, or >20 kg: 20 mg/d (n = 23, mean NS [10 mg/dl; n = 29, mean NS [20 mg/d])	8 wk (LFU: 0 of 109 [0%])	AEs: n = 82; TRAEs, most common: diarrhea (3), headache (2), and somnolence (2); differences between groups, not significant; PGA vs baseline, P < .005 (all groups); change in symptoms according to PGA: parents scores vs baseline, P < .01 (all groups); assessment by parents, significant differences between groups: NS
Boccia et al[34] (2007), high quality (7.5)	General pediatric practice; children (32–170 mo old) with GERD and reflux esophagitis in endoscopy-confirmed remission treated with omeprazole (1.4 mg/kg per d) for 3 mo	Omeprazole: 50% of starting dose (1.4 mg/kg per d) (n = 16, 86 ± [NS] mo)	Ranitidine: 10 mg/kg per d or no treatment (No) (n = 16, 98 ± [NS] [ranitidine]; n = 14, 105 ± [NS] mo [No])	Open label: 3 mo; double-blind: 6 mo; follow-up: 33 mo (LFU: 2 of 48 [4%])	Change in endoscopic healing and symptom score (daily dairy parents and at each clinical visit); no statistically significant difference between groups; significant reduction in histological (P = .02), endoscopic (P = .01), and symptomatic scores (P = .004) in all study groups compared with baseline
Borreli et al[35] (2002), low quality (5)	General pediatric practice: children (1–12 y old) with GERD symptoms combined with results of pH monitoring and/or moderate esophagitis shown on endoscopy	Lansoprazole: 2 × 1.5 mg/kg per d; lansoprazole + alginate (LanAl); (n = 10, mean NS [lansoprazole]; n = 12, mean NS [LanAl])	Alginate: 2 mL/kg per d (n = 10, mean NS)	8 wk (LFU: 4 of 36 [11%])	Change in clinical symptom scores: alginate, 4.2 ± 0.9; lansoprazole, 4.3 ± 1.2; LanAl, 3.0 ± 1.1; LanAl vs alginate and lansoprazole, P < .05; alginate/lansoprazole/LanAl vs baseline, P < .01; reduction in esophageal acid exposure time: alginate, 6.1 ± 1.9; lansoprazole, 5.5 ± 1.5; LanAl, 3.8 ± 0.7; LanAl vs alginate and lansoprazole, P < .05; alginate/lansoprazole/LanAl vs baseline, P < .01; intragastric acidity: alginate, 2.5 ± 0.6; lansoprazole, 3.9 ± 0.3; LanAl, 4.2 ± 0.8; lansoprazole and LanAl vs baseline, P < .01; Al vs baseline, P = .08; endoscopic healing: all groups (significance NS)

TABLE 2 Continued

Study and Quality	Setting, Participants, Diagnosis	Intervention (No. of Participants, Age, Mean ± SD)	Control Intervention (No. of Participants, Age, Mean ± SD)	Follow-up	Outcome Measures and Results
Cucchiara et al[36] (1993), low quality (5.5)	General pediatric practice; children (6 mo to 13.4 y old) with GER esophagitis based on pH monitoring, endoscopy, and histology; unresponsive to ranitidine (2 × 8 mg/kg per d) and cisapride (3 × 0.8 mg/kg per d).	Omeprazole: 40 mg/d per 1.73 m² body surface area (n = 16, mean NS)	Ranitidine: 20 mg/kg per d (n = 16, mean NS)	8 wk (LFU: 2 of 32 [6%])	Reduction in median gastric pH: omeprazole, 60.1 (9.3–81); ranitidine, 37.4 (0–56.7) (P < .05); change in symptom score: omeprazole, 9.0 (0–18) (P < .01); ranitidine, 9.0 (6–12) (P < .001); significant difference between groups: NS; omeprazole, 2.0 (0–6) (P < .01); ranitidine, 2.0 (2–6) (P < .01); change in esophagitis score (by endoscopy and histology): significant difference between groups: NS
Adolescents					
Tsou et al[37] (2006), high quality (9)	General pediatric practice; adolescents (12–16 y old) with a CSS of >16 on the GASP-Q, clinical diagnosis of suspected symptomatic, or endoscopy-proven GERD	Pantoprazole: 20 mg/d (n = 68, 13.9 ± 1.37 y)	Pantoprazole: 40 mg/d (n = 68, 14.1 ± 1.37 y)	8 wk (LFU: 6 of 136 [4%])	Change in GASP-Q in mean CSS: CSS, 20 mg/d, 177.7 vs 67.2 (P < .001); 40 mg/d, 174.1 vs 58.2 (P < .001); no significant changes between study groups; AEs: NS (no serious AEs); mild/moderate TRAEs: 20 mg/d, 59 (87%); 40 mg/d, 53 (78%); most common: headache (35%), infection (23%), and pharyngitis (19%); no significant differences between groups
Gold et al[38] (2007), high quality (8.5)	General pediatric practice; adolescents (12–17 y old) with clinical diagnosis of GERD based on medical history, physical examination, pH monitoring, and/or endoscopy and biopsy	Esomeprazole: 20 mg/d (n = 76, mean NS)	Esomeprazole: 40 mg/d (n = 73, mean NS)	8 wk (LFU: 4 of 149 [3%])	AEs: 113; TRAEs (14.9% of patients): most common: headache (8%), abdominal pain (3%), and diarrhea (2%); no significant differences between groups; reduction of GERD symptoms according to PGA: no significant changes between groups; symptoms were significantly reduced compared with baseline (P < .0001)

NS indicates not stated; LFU, lost to follow-up; I-GERQ-MH, Infant Gastroesophageal Reflux Questionnaire Revised Medical History; GAS, Global Assessment Score; GSQ-I, GERD Symptom Questionnaire Infants; PMA, postmenstrual age; I-GERQ-R, Infant Gastroesophageal Reflux Questionnaire Revised; HF, hydrolyzed formula; CSS, composite symptom score; GASP-Q, Gastroesophageal Reflux Assessment of Symptoms in Pediatrics Questionnaire; ISS, individual symptom score; PGA, Physician Global Assessment.

One study did not report on AEs, only TRAEs.[37] TRAEs in that study included headache (35%), infection (23%), and pharyngitis (19%). The other study[38] did report on AEs and TRAEs, of which headache (8%), abdominal pain (3%), and diarrhea (2%) were the most frequently reported TRAEs. No significant differences of AEs and/or TRAEs were detected between the studied groups in both studies.

DISCUSSION

This SR reveals that PPIs are not effective in reducing GERD symptoms in infants. Although SRs and placebo-controlled studies are lacking in children and adolescents, randomized trials have shown PPIs to be equally effective in reducing GERD symptoms compared with their controls (alginates, ranitidine, different-dosage PPIs). It is not surprising that PPIs are effective in reducing gastric acidity in all age groups. However, the effect of PPIs on histologic aberrations in children with GERD is unclear, because only 3 studies in our review reported on the differences in histologic scores between the studied groups, and no differences were found in 2 of them. On balance, short-term use of PPIs was well tolerated, although 1 study did reveal a significant change in lower respiratory tract infections. Evidence to ensure safety is still lacking. AEs tend to be of a mild-to-moderate nature; headache is the most frequently reported TRAE.

Because of statistical and clinical heterogeneity of the included studies, we were not able to perform a pooled analysis with a fixed- or random-effect model. Well-designed RCTs, especially the placebo-controlled trials, with a high methodologic quality were sparse, and sample sizes were often small.[27–29,32,34–36] Furthermore, methodologic quality scores of the included studies were determined by the Delphi

list. Although this is a validated list, it lacks any consideration of the number of included subjects. A plausible explanation of the small sample sizes in this review could be that performing placebo-controlled studies on infants and children is regarded to be unethical, not only by medical ethical committees but also especially by parents who often refuse to have their child participate in placebo-controlled trials because of the "risk" of being assigned to the placebo arm. Furthermore, invasive procedures such as blood-testing, combined impedance-pH measurement, and/or endoscopy are required to be part of the study protocol, and parents are often hesitant to agree to their infant enduring such procedures. Finally, placebo-controlled studies often take place in academic centers, whereas GERD-related problems are mainly treated in nonacademic centers, which makes it more difficult to include patients. Nonetheless, it is well-known that pharmacodynamics, pathophysiology, and symptom presentation might differ substantially between children and adults. For example, dosage and delivery method, the latter especially in frequently fed infants, may vary substantially. Furthermore, evidence of effectiveness of PPIs in adults[21] cannot be extrapolated to children. Thus, it could be argued that it is unethical to prescribe drugs without convincing evidence for efficacy of therapy in the age group to be treated.

Another problem that influenced meaningful comparisons between studies is that the criteria used for randomization varied greatly from study to study (eg, pH-monitoring acid-exposure criteria[27] versus symptom-frequency criteria[30]). In both of these cases, diagnostic criteria used to justify randomization were defined on the basis of a "best guess" rather than previous validation. More precise diagnostic testing methods such as pH-

impedance monitoring are now available. These tests, in theory, offer the potential for antireflux therapy to be better targeted at patients in whom symptom episodes can be demonstrated to be caused by acid GER and/or bolus GER by using symptom-association probability.[9] It is unfortunate that despite what seems to be an improvement in diagnostic methodology, there have been no published reports from studies that have randomly assigned patients on the basis of this approach; therefore, it remains to be determined if positive symptom-association criteria are truly meaningful.

The included studies had several drawbacks. First, in the infant studies, 2 of the RCTs had a crossover design,[27,28] which indicates that PPI- or placebo-treated subjects acted as their own controls. Immediate withdrawal of PPIs may trigger a rebound effect of hypersecretion of gastric acid,[39,40] thereby influencing study results. However, it could also be argued that the dosing period before outcome measures were recorded was sufficiently long to nullify any of the acute affects caused by acid rebound.

Second, we included 2 infant studies that implemented an open-label phase with a PPI during the study period (1 before[31] and 1 after[30] randomization). Despite the fact that the authors of both studies described results of the open-label phase separately, use of a PPI before randomization also could have influenced study outcome. In the study by Winter et al,[31] they observed a rapid worsening of symptoms in patients switched from a PPI directly to placebo. Acid rebound seems the likely genesis of this response. Both in the crossover studies[27,28] and the open-label study[31] this possible risk of a rebound effect was not discussed.

Third, in 1 of the included study reports a significant decrease in GERD

symptoms was described[29] compared with symptoms of those who were on hydrolyzed formula. Although the study met our inclusion criteria, the methodologic quality was relatively poor. Besides that, the study protocol lacked data with respect to follow-up. Therefore, it remains unclear whether GERD symptoms relapsed over time in the PPI and placebo groups. Another drawback of this study is that infants were included on a reflux questionnaire solely. Questionnaires represent self-reporting behavior and, in this case, the caregivers' judgment on their infant's condition. Using a reflux questionnaire for the inclusion of patients without other tools to diagnose GERD is questionable, because this tool may not be of good value in the prediction of severity of GERD.[41] It is well known that symptoms such as crying and irritability are nonspecific, and the presence of GERD and these symptoms may not always correlate.[42,43]

Fourth, the included studies that involved children and adolescents, although randomly controlled and of high methodologic quality, were not placebo-controlled, which makes the results difficult to interpret. Four of these were dose-finding studies.[32,33,37,38] As previously mentioned, no differences in efficacy were found between the different dosages of PPIs at the end of the studies. However, symptom resolution was achieved more rapidly in the higher-dosage groups in 2 studies (20 and 40 mg compared with 10 mg[32] and 40 mg compared with 20 mg[37]). In another study that evaluated maintenance therapy,[34] both study groups were treated with a PPI before random assignment during 3 months, which also could have influenced the study results. The studies that used ranitidine[34,36] and alginates[35] as a control group revealed reduction in GERD symptoms in all studied groups compared with baseline. However, 1 study

used 3 different treatment arms[35] and compared the effect of the alginate and PPI alone or in combination. It is interesting to note that this study found a statistically significant difference between the combination arm and single-treatment arms.

Finally, in the 3 studies from which histologic alterations and endoscopic scores were described,[34–36] healing was seen in subjects in all study groups compared with baseline. However, a clear description of the biopsy analysis was lacking, and no data were provided regarding the place and the number of biopsies taken. The use of an international classification of esophagitis would make results easier to interpret. Also, the data described in 2 study reports[35,36] were not supported by statistical analysis, which makes interpretation difficult. Overall, the role of histology as an outcome measure is under debate. A recent natural history study by Orenstein et al[44] identified infants with GERD and esophagitis who showed complete or nearly complete symptom resolution without pharmacotherapy, and there was a remarkable finding of no histologic alterations.

A decrease in GERD symptoms was described for the majority of patients in both treatment arms.[28,31,32–36,37,38] Because in 58% of the studies a placebo group was lacking, the value of this outcome is questionable. It is well known that resolution of symptoms could be a result of spontaneous symptom resolution over time, the symptoms reported simply not being associated with GERD but the result of other reasons, or a high placebo effect.[5,45,46]

It is interesting to note that studies that involved adults with GERD have revealed the effectiveness of PPIs in the decrease of GERD symptoms.[47,48] Discrepancy between the findings in infants and adults could be a result of the fact that symptoms in adults are more distinct and better expressed than in infants. Because PPIs act solely as acid inhibitors, whereas in milk-fed infants gastric contents are nonacidic during a large part of the day, the poor effect of PPIs in this age group on GERD symptoms might be predicted.

Although GERD symptoms in children and adolescents resemble those in adults, PPIs in these age groups are equally effective compared with their controls (alginates, ranitidine, or different dosages of PPIs). Why these results might be a result of the lack of placebo-controlled studies and the possibility that young children and their parents are less accurate when reporting symptoms.[49,50] Furthermore, in adults, esophagitis is more likely to exist than in children and adolescents, possibly because of long-term esophageal acid exposure.

Orenstein et al[30] found significantly more serious AEs in the PPI group compared with the placebo group. These differences, however, were judged by the clinicians treating the individual subjects and seemed not to be treatment related. When addressing AEs, as reported for the 2 adolescent studies, we noted a remarkable difference between the reported AEs in both studies (eg, headache, 35%[37] compared with 8%[38]). A possible explanation for this

difference could be the intraobserver variability of the caregiver when judging an AE as being treatment related. With respect to short-term and long-term use of PPIs, we included studies from which only short-term AEs were reported. In this review, sample sizes were small, and the methodologic quality of the exploration of AEs and TRAEs was sparse and poorly described. We found 1 study for which long-term use of PPIs was described,[17] but it was a retrospective study and, therefore, excluded from our evaluation.

CONCLUSIONS

If the primary aim is to treat GERD symptoms in infants, PPIs should not be prescribed. Despite PPIs seeming to be well tolerated in the short-term, there is insufficient evidence to support the effectiveness and safety of PPIs in the treatment of GERD in children and adolescents. Therefore, physicians should be careful when prescribing PPIs, medications that are not approved for infants and have potential adverse effects, unless there is documented disease or with careful monitoring. Large, well-designed, placebo-controlled, randomized trials with well-chosen end points are necessary to evaluate the effect and safety of PPIs in the entire pediatric age range. Furthermore, we recommend more pathophysiological research on symptom genesis to be able to clearly define homogeneous patient groups and to enable the development of a therapy to tackle this growing health care problem.

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ZINC FOR THE COMMON COLD: *When my kids get a cold and ask what they can do to feel better, I recommend drinking plenty of fluids and tincture of time (which rarely pleases them). Now, I might be able to make a different recommendation. According to an article in* The New York Times *(U.S.: February 11, 2011), zinc might be beneficial not only to treat but also to prevent the common cold. The utility of zinc for the treatment of the common cold has been debated since a publication in 1984 showed beneficial effects to frequent zinc administration. Since that time, 11 of the subsequent 18 trials of zinc preparations for the treatment of the common cold have demonstrated benefit. A recent publication in the Cochrane Database of Systematic Reviews concluded that zinc, when taken within 24 hours of the first signs of a cold, can reduce the duration of cold symptoms by a day and decrease the severity of the symptoms. Regular zinc administration to children led to fewer colds and school absences, and less antibiotic use. Researchers came to their conclusion after pooling the data from 15 studies that had enrolled almost 1400 participants. How zinc decreases cold symptoms is unknown. While researchers concluded that zinc is beneficial for the treatment of the common cold, they failed to recommend a dose, ionic state, or formulation most likely to work. The problem for consumers is that effectiveness of zinc may depend on all these factors and little is known how effective one dose or formulation might be. Also, individuals will need to be fairly motivated as a popular zinc acetate lozenge is to be taken every three to four hours. Moreover, some preparations have an unpopular, bitter taste. So while my kids may be excited about trying different zinc preparations for their cold symptoms, fluids and time are still likely to be good advice.*

Noted by WVR, MD

Efficacy of Proton-Pump Inhibitors in Children With Gastroesophageal Reflux Disease: A Systematic Review

Rachel J. van der Pol, Marije J. Smits, Michiel P. van Wijk, Taher I. Omari, Merit M. Tabbers and Marc A. Benninga

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