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REVIEW ARTICLE

Comparative Safety and Efficacy of Proton Pump Inhibitors in Paediatric Gastroesophageal Reflux Disease

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Abstract Gastroesophageal reflux is one of the most common reasons for referrals to paediatricians or paediatric gastroenterologists. Gastric acid-buffering agents, mucosal surface barriers and gastric anti-secretory agents are the main groups of medications currently used for treating gastroesophageal reflux disease (GERD) in children. Recently, the use of proton pump inhibitors (PPIs) for the treatment of GERD in children has increased considerably. Their effectiveness in healing erosive oesophagitis in paediatric subjects and in improving GERD symptoms has been established in many studies. However, the effectiveness in other clinical conditions and the long-term safety of PPIs for paediatric GERD have not been fully established yet and thus are still under debate. Therefore, the aim of this article is to provide a comparative review of the efficacy, safety and tolerability of PPIs in paediatric GERD. The available data suggest that short-term use of PPIs is well tolerated. Adverse events tend to be of a mild-to-moderate nature, with headache being the most frequently reported treatment-related adverse event. However, further well-designed trials and observational studies are still needed to clarify the efficacy and safety of PPIs in the paediatric population, especially in infants under the age of 12 months.

Key Points

Proton pump inhibitors (PPIs) are not effective in reducing gastroesophageal reflux disease (GERD) symptoms in infants.

Use of PPIs in the treatment of GERD symptoms and in healing of erosive disease has been well documented in both children and adolescents.

Although PPIs seem to be well tolerated during short-term use, the evidence supporting their long-term safety is lacking.

1 Introduction

Gastroesophageal reflux is a common but usually self-limiting and non-pathological condition of young infants. Gastroesophageal reflux disease (GERD) refers to persistent reflux caused by pathological factors and resulting in significant symptoms. Patients may present with oesophagitis, bleeding, nutritional failure or respiratory problems [1]. The aim of GERD therapy is to reduce gastric reflux, relieve symptoms, manage complications and prevent recurrence. The treatment algorithm is a stepwise process; it begins with lifestyle modifications, and pharmacotherapy is introduced later if conservative management is not effective. Although various drugs can be used to reduce acidity, stimulate oesophageal peristalsis and preserve the oesophageal mucosa, gastric acid-buffering agents, mucosal surface

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barriers and gastric anti-secretory agents are the most frequently prescribed treatments in these indications [2].

Proton pump inhibitors (PPIs; omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole) inhibit gastric acid secretion through selective blockade of the gastric parietal cell H^+K^+ adenosine triphosphatase (ATPase; also referred to as the proton pump), an enzyme that is involved in the last step of acid secretion in gastric parietal cells. The prevalence of peptic acid diseases has greatly increased in both adults and children, and thus the use of PPIs has widely expanded during recent decades [1]. As a result, PPIs have became one of the most frequently prescribed medications for treating both adults and children [3].

Effectiveness of PPIs in the treatment of peptic conditions, such as gastric ulcers, GERD and *Helicobacter pylori* infections, has been shown in paediatrics, but there is still a lack of long-term safety data in children older than 1 year [4–6]. Although there have been studies in populations of neonates and infants to identify the doses that inhibit acid production, the efficacy of PPIs in the treatment of GERD has not been established in these groups, except for the recent approval of esomeprazole treatment for erosive oesophagitis in infants. PPIs are generally well tolerated in the paediatric population [7]. However, their certain shortcomings, such as increased susceptibility to acute gastroenteritis and community-acquired pneumonia [8], respiratory infections [9], gastric polyps [10] and bacterial overgrowth [11], have been reported. Therefore, although PPIs are widely considered the most effective acid-suppressive therapy for adults with GERD [12], their efficacy and safety profiles in the paediatric population are less clear.

PPIs are frequently used without any specific diagnostic testing in infants and children. Therefore, correct indications for the use of PPIs in these groups need to be established, with respect to the specific nature of their pharmacodynamics, pharmacokinetics and bioavailability in paediatrics. The aim of this article is to review the current literature on the efficacy, safety and tolerability of various PPIs in infants and children with GERD.

The indications for PPI use in children, according to Romano et al. [13], are as follows: healing of acute erosive oesophagitis; maintenance of remission in patients with erosive oesophagitis; and symptomatic relief of non-erosive reflux disease, nocturnal acid secretion and relevant reflux, and supra-oesophageal symptoms of GERD. Only the first indication (acute erosive oesophagitis) refers to infants.

2 Systematic Review of the Efficacy of PPIs in Children with GERD

In 2011, a systematic review of the efficacy of PPIs in children with GERD was published in *Pediatrics* [14]. The report included 12 studies conducted in Europe, Australia and North America; ten of them were randomized controlled trials (RCTs) and two were crossover trials. A total of 895 participants (aged 0–17 years) were enrolled. The studies included in this systematic review were subdivided on the basis of the age of the investigated population (infants: 0–1 years old; children: 1–13 years old; and adolescents; 13–18 years old) because of the different presentations of GERD symptoms in these categories and, therefore, possible differences in efficacy. The review demonstrated that PPIs are not effective in reducing GERD symptoms in infants, and it emphasized the lack of placebo-controlled trials in older children. Moreover, the review indicated that although PPIs seem to be well tolerated during short-term use, the evidence supporting their safety is lacking [14].

3 Literature Review

We searched Medline, PubMed, the Cochrane Database of Systematic Reviews electronic database and the Cochrane Controlled Trials Register for systematic reviews, RCTs and crossover studies from inception to December 2013. 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); '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. The reference lists of reviews and included studies were searched by hand to identify additional studies.

3.1 Study Selection

The inclusion criteria were as follows: (1) the study was a systematic review, RCT or crossover study; (2) the study population consisted of children aged 0–18 years with GERD and/or oesophagitis; (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 oesophagitis, children who had undergone surgical therapy or children who had previous use of any other therapy besides PPIs (such as histamine H2 receptor antagonists, 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.

4 Pharmacokinetics of PPIs in Paediatrics

Although they are similar in structure, the various PPIs differ in terms of their metabolism. They are metabolized by the hepatic cytochrome P450 (CYP) enzymatic system, especially by the CYP2C19 enzyme. As the expression of CYP2C19 has been demonstrated to be under genetic control [15], the pharmacokinetics and pharmacodynamics of PPIs depend on the CYP2C19 genotype status. Compared with individuals who represent a rapid extensive metabolizer (RM) phenotype for CYP2C19, poor metabolizers (PMs) have substantially greater exposure (increased plasma concentrations) from a therapeutic dose of a PPI. Therefore, the differences in PPI biotransformation associated with polymorphism of drug-metabolizing enzymes contribute to specific disposition characteristics in paediatric patients.

4.1 Pharmacokinetics in Infants

Previous studies have revealed that neonates display reduced metabolic capacity and clearance of both omeprazole and lansoprazole [16]. Moreover, immaturity of drug-metabolizing CYP2C19 and CYP3A4 enzyme pathways has been reported in both pre-term infants and full-term neonates [17, 18], which may account for the greater systemic exposure to PPIs in this population than in older children [19–21]. Since determination of the pharmacodynamic response to PPIs in infants with GERD is crucial to select the appropriate dose for their efficacy, Kierkus et al. [22] analysed the pharmacodynamics and safety of pantoprazole in neonates, pre-term infants and infants aged 1–11 months with a clinical diagnosis of GERD. In these two open-label studies, neonates and pre-term infants (study 1: ~1.2 mg/kg, i.e. high dose), and 1- to 11-month-old infants (study 2: ~0.6 mg/kg, i.e. low dose, or ~1.2 mg/kg, i.e. high dose) received pantoprazole once daily [22]. Twenty-four-hour dual-electrode pH-metry parameters were compared between pre-dose and steady state (≥5 days), using a two-sided paired *t* test. The treatment was administered for ≤6 weeks. The authors demonstrated that a high dose of pantoprazole improved pH-metric parameters after ≥5 consecutive daily doses and was generally well tolerated for ≤6 weeks.

4.2 Pharmacokinetics in Children and Adolescents

Unlike infants, children aged 1–6 years presented with increased metabolic capacity. Andersson et al. [23] examined the dose, safety, efficacy and tolerability of orally administered omeprazole in children with erosive oesophagitis and pathological acid reflux. The pharmacokinetics of omeprazole showed a trend towards higher metabolic capacity with decreasing age, being highest at 1–6 years of age. This may explain the need for an increased weight-adjusted dose of PPIs in this age group. In a study conducted in 12- to 16-year-old adolescents, the pharmacokinetic properties of rabeprazole were similar to those reported for adults [24].

5 PPI Use in Infants

The number of PPIs prescribed for infants has significantly increased in recent years, despite the absence of evidence for acid-related disorders [1, 25]. Although some trials on various PPIs in infants aged <1 year included pre-term infants and newborns (aged 0–1 month) [26–29], no PPI is approved for treatment of non-erosive GERD in children younger than 1 year of age.

First of all, there are only sparse data on the normal range of serum gastrin levels in infants. While it has been demonstrated that the mean fasting gastrin level in adults with GERD was higher than that in healthy controls [30]. Treem et al. [31] assessed normal and proton pump inhibitor-mediated gastrin levels in 1- to 11-month-old infants. The authors demonstrated that gastrin levels in treatment-naïve infants were elevated through 8 months of age. However, they declined to the median level within the upper limit of the normal adult range (<100 ng/L) between 8 and 12 months of age. Moreover, the study showed that previous exposure to acid-suppressive medications and short-term exposure to rabeprazole significantly increased gastrin levels in infants younger than 1 year [31]. These findings are consistent with the outcomes of PPI efficacy studies in infants. A double-blind placebo-controlled trial of omeprazole in irritable infants with oesophagitis or a reflux index >5 % found no difference in the duration of crying between the experimental and placebo arms, despite highly effective acid suppression in the omeprazole-treated group [32]. Another trial, a large double-blind study of 162 infants randomized to receive 4 weeks of placebo or lansoprazole, revealed an identical 54 % response rate in each group, using >50 % reduction of measures of feeding-related symptoms (crying, irritability, arching and other parameters of the Infant Gastroesophageal Reflux Questionnaire [I GERQ] as an endpoint [27]. Similar results have also been demonstrated in studies of the use of pantoprazole and esomeprazole in infants [33–35]. Although an improvement of symptoms during the open-label run-in period was reported, no statistically significant difference between the PPI and placebo groups was noted during the withdrawal phase [33–35].

The available evidence does not support empirical use of acid-suppressing medications in infants with unexplained crying, irritability or sleep disturbance [36]. This may be explained by the infants' immaturity and/or physiological reflux, which does not need pharmacological therapy and improves with time. Many children with clinically diagnosed GERD may have physiological reflux and do not need any pharmacotherapy at all. Springer et al. [28] analysed the effect of lansoprazole in infants and pre-term infants with GERD symptoms, and reported similar profiles of changes in pH-metry parameters and gastric pH in both the treated and placebo groups. Omari et al. [36] studied the effect of omeprazole on pH-metry parameters and symptoms in ten pre-term infants enrolled on the basis of symptoms and a reflux index >5 %. The patients received treatment with either omeprazole or placebo for 7 days each in a crossover fashion. The authors reported no improvement in symptoms despite normalization of the reflux index, which only confirmed the dissociation between oesophageal pH-metry and symptoms [36]. Hussain et al. [37] studied the efficacy and safety of rabeprazole in 1- to 11-month-old infants with symptomatic GERD that was resistant to conservative therapy and/or previous exposure to acid-suppressive medications. A total of 344 participants were enrolled in a 1- to 3-week open-label phase and received rabeprazole (10 mg/day). Following caregiver-rated clinical improvement during the open-label phase, patients were randomized to receive placebo, rabeprazole 5 mg or rabeprazole 10 mg in the ensuing 5-week double-blind withdrawal phase. The following endpoints were analysed: frequency of regurgitation; weight-for-age *Z* scores; and daily and weekly GERD symptom scores. The authors concluded that the improvements in symptoms and weight were similar in all three analysed treatment arms [37].

In view of the aforementioned evidence, the problem with the use of PPIs in infants may stem from difficulties in accurate quantification of the symptoms presented by this group of patients, as well as from the confirmation of the relation between symptoms and reflux of gastric contents into the oesophagus. Moreover, the symptoms may be non-specific and unrelated to reflux disease, but they may develop secondarily to functional conditions without organic pathology (so-called happy spitters) [38] or secondarily to allergy to cow's milk [39]. These clinical conditions provide no indication for PPI use in infants.

6 PPI Use in Children and Adolescents

Contrary to the indications in infants, the indications for PPI use in children are clearer. Since high efficacy of PPIs in the treatment of GERD symptoms and healing of erosive disease has been well documented both in adults and in children [12], these drugs are indicated for treatment of GERD in patients of all ages beyond infancy. Other clinical indications for use of PPIs include peptic ulcer disease and related complications, such as gastrointestinal bleeding, *Helicobacter pylori* infection and Barrett's oesophagus [40]. The most important indication for use of PPIs is treatment of erosive oesophagitis, re-named according to the new classification by Sherman et al. [41] as 'typical erosive reflux syndrome', a specific condition in children under 8 years of age. In adolescents (children aged 13–18 years) the indications for use of PPIs are similar to those in adults, and non-erosive GERD is the most common reason for their prescription.

The optimum dosage regimen for most PPIs, except for rabeprazole, is for them to be taken 15–30 min before breakfast. Rabeprazole can be taken with or without food. Since abrupt discontinuation of treatment with a PPI may result in acid rebound and resultant precipitation of symptoms in some patients, anti-secretory therapy should be discontinued slowly [42, 43]. A systematic review [14], including 12 studies on the effectiveness and safety of PPIs in children with GERD, has identified four trials in which these agents were more effective for gastric acidity than placebo, alginic acids or ranitidine. In three of the studies, PPIs did not differ from ranitidine or alginic acids in reducing histological aberrations. Furthermore, six trials documented no differences in treatment-related adverse events (compared with placebo or a different PPI dosage) [14]. Haddad et al. [44] evaluated the efficacy and safety of rabeprazole in 1- to 11-year-old children with endoscopically/histologically proven GERD in a multicentre, double-blind, parallel-group study. The children were randomized to receive a 0.5 or 1.0 mg/kg rabeprazole granule formulation for 12 weeks, with further dose determination by weight. The study revealed that rabeprazole is effective and safe in 1- to 11-year-old children with GERD [44]. A recent study by the same group [45] has additionally determined the efficacy and safety of maintenance therapy with rabeprazole in 1- to 11-year-old children with endoscopically proven GERD. Healing was maintained in 90 % of the children (100 % of the low-weight cohort, 89 % of the 10 mg high-weight cohort and 85 % of the 20 mg high-weight cohort) [45].

Table 1 summarizes a number of available trials and efficacy data for each PPI separately.

7 Safety of PPIs in Infants

A total of five placebo-controlled studies analysed the efficacy and/or safety of PPIs (lansoprazole [27, 46], omeprazole [32, 36] and pantoprazole [29]) in infants with

Table 1 Number of available trials and efficacy data for each proton pump inhibitor (PPI) separately

PPI	Number of studies	Efficacy
Infants		
Omeprazole	1	No difference[a]
Rabeprazole	1	No difference[a]
Esomeprazole	1	No difference[a]
Lansoprazole	2	No difference[a]
Pantoprazole	0	
Children		
Omeprazole	2	Effective[a]
Rabeprazole	2	Effective[a]
Esomeprazole	1	No difference[a]
Lansoprazole	1	Effective[a]
Pantoprazole	2	No difference[a]

[a] Symptom decrease/reduction in reflux index compared with placebo/other anti-reflux drug

GERD aged under 12 months. A multicentre, double-blind, randomized, placebo-controlled trial [27] documented at least one treatment-emergent adverse event in 62 % of lansoprazole-treated infants with GERD and in 46 % of placebo recipients ($p = 0.058$). Serious adverse events, mainly lower respiratory tract infections, occurred in 12 infants and were significantly more frequent in the lansoprazole group than in the placebo group (10 versus 2, $p = 0.032$) [27].

Esomeprazole has already been approved by the US Food and Drug Administration for use in infants 1–12 months of age. In an 8-week, multicentre, randomized, uncontrolled, double-blind study by Gilger et al. [47] to evaluate the safety, tolerability and symptom improvement with once-daily esomeprazole in children aged from infancy to 11 years with endoscopically proven GERD, all doses of esomeprazole were well tolerated. The most common adverse events judged by the investigator as being treatment related were diarrhoea, somnolence and headache. In total, 82 patients (75.9 %) had 311 adverse events, regardless of causality. The most common adverse events were vomiting, pyrexia and diarrhoea. A total of 13 treatment-related adverse events, as judged by the investigator, were reported by 10 patients (9.3 %). There were no deaths. Two patients who received esomeprazole 10 mg (one child in each weight stratum) experienced serious adverse events (vomiting) during the treatment period. One patient who weighed ≥20 kg and received esomeprazole 20 mg had a serious adverse event during the screening endoscopy (airway complication of anaesthesia). No serious adverse events were considered by the investigator to be related to treatment. A total of three patients discontinued participation in the study because of adverse events: one patient who weighed <20 kg and received esomeprazole 10 mg experienced vomiting and hypertension (which were judged by the investigator as not related to the study medication); and two patients who weighed ≥20 kg and received esomeprazole 10 mg experienced erythema multiforme, urticaria and eye swelling (which were judged by the investigator as not related to the study medication); and asthenia, nausea and symptoms of viral infection (which were judged by the investigator as possibly related to the study medication), respectively. The adverse events that were judged by the investigator as being possibly related to the treatment and resulted in study discontinuation (i.e. asthenia, nausea and symptoms of viral infection) resolved within 1 day of onset, after administration of the study drug was stopped. No clinically important changes in any clinical laboratory values, urinalysis, vital signs or physical examination were reported [47]. In a placebo-controlled treatment-withdrawal study by Winter et al. [29], assessing the efficacy and safety of pantoprazole delayed-release granules for oral suspension in infants aged 1–11 months with symptomatic GERD, adverse events leading to discontinuation during the open-label phase were diarrhoea in one patient, excessive crying in one patient and worsening of 'GERD symptoms' in two patients. During the double-blind phase, one patient discontinued participation in the study because of sleep problems. Eight patients had one or two serious adverse events during the study, of which five occurred during treatment with pantoprazole. All serious adverse events were considered unrelated to the treatment by the investigators. Treatment-emergent adverse events reported in ≥5 % of patients during the open-label phase were upper respiratory infection in 25 patients (19.5 %), fever and diarrhoea in 13 patients (10.2 %) each; otitis media in 12 patients (9.4 %); rhinitis in 11 patients (8.6 %); contact dermatitis/cutaneous moniliasis (diaper rash) in 10 patients (7.8 %); and vomiting, oral moniliasis and cough increased in 7 patients (5.5 %) each. The events were mild or moderate in severity, as assessed by the investigators, with the exception of two severe adverse events (gastroenteritis and failure to thrive). During the double-blind phase, upper respiratory infection was the most commonly reported treatment-emergent adverse event in each treatment group, occurring in seven patients (13.0 %) in each group. All events were mild or moderate in severity; no between-group differences were noted in the incidence and severity of adverse events during this phase [29]. In the study by Khoshoo et al. [46] evaluating clinical response to two dosing regimens of lansoprazole in infants with GERD, the authors concluded that both treatment regimens were well tolerated, and there were no clinical adverse reactions.

8 Safety of PPIs in Children and Adolescents

Five well-designed studies analysed the efficacy and safety of esomeprazole [14], lansoprazole [48], omeprazole [49, 50] and pantoprazole [51] in children with GERD. All studies revealed that the PPIs were as effective as the treatments administered in the control arms and significantly reduced GERD symptoms in all of the groups. Mild-to-moderate adverse events, headache ($n = 6$) and diarrhoea ($n = 3$) were documented in two studies [10, 14]. Another open-label, single- and multiple-dose study of the pharmacokinetic and safety profile of rabeprazole sodium tablets in children and adolescents with GERD reported headache and nausea (16.7 and 8.3 %, respectively) as the most frequent adverse events, with no significant differences between the dose groups [45]. Haddad et al. [45, 46] analysed the efficacy and safety of 12-week therapy and maintenance therapy with rabeprazole in 1- to 11-year-old children and reported a 63 % overall incidence of treatment-emergent adverse events. The most commonly reported (>10 %) adverse events included cough and vomiting (14 % each), abdominal pain (12 %) and diarrhoea (11 %) with 12-week therapy, and upper respiratory tract infections (13 %) and vomiting (11 %) with maintenance treatment [45, 46].

Two studies analysed the efficacy of esomeprazole [52] and pantoprazole [53] in 12- to 17-year-old adolescents with GERD. In a multicentre, randomized, double-blind study comparing 20 and 40 mg of pantoprazole, this agent turned out to be safe, well tolerated and effective in reducing symptoms of GERD in 12- to 16-year-old adolescents, irrespective of the dose [53]. Gold et al. [52] assessed the safety of esomeprazole (20 or 40 mg once daily) in adolescents with clinically confirmed GERD and documented treatment-related and non-treatment-related adverse events in 75 % and 78 % of patients in the esomeprazole 20 mg and 40 mg groups, respectively. Twenty-two patients (14.9 %) experienced adverse events that were considered to be related to the treatment; the most common were headache (8 %, 12/148), abdominal pain (3 %, 4/148), nausea (2 %, 3/148) and diarrhoea (2 %, 3/148). No serious adverse events or clinically important findings in other safety assessments were observed [52].

The most important safety issues are tabulated in Table 2.

Table 2 The most important safety issues for each proton pump inhibitor (PPI) according to age group

PPI	Important safety issue	Age group
Lansoprazole	Lower respiratory tract infections	Infants
Esomeprazole	Diarrhoea	Infants
Pantoprazole	Diarrhoea	Infants
Pantoprazole	Upper respiratory tract infections	Infants
Rabeprazole	Vomiting	Children (1–11 years old)
Rabeprazole	Abdominal pain	Children (1–11 years old)
Rabeprazole	Diarrhoea	Children (1–11 years old)
Esomeprazole	Abdominal pain	Adolescents
Esomeprazole		Adolescents

9 Conclusions

The available data suggest that short-term use of PPIs is well tolerated in both infants and children older than 1 year. Adverse events tend to be of a mild-to-moderate nature, with headache being the most frequently reported treatment-related adverse event in older children and adolescents. However, emerging evidence suggests that these widely prescribed medications may not be as benign as previously believed. Therefore, further well-designed trials and observational studies are needed to clarify the efficacy and safety of PPIs in the paediatric population, especially in infants under 12 months of age [13].

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References

1. Orenstein SR, Izadnia F, Khan S. Gastroesophageal reflux disease in children. Gastroenterol Clin N Am. 1999;28:947–69.
2. Yellon RF, Goldberg H. Update on gastroesophageal reflux disease in pediatric airway disorders. Am J Med. 2001;111(Suppl 8A):78S–84S.
3. Barron JJ, Tan H, Spalding J, Bakst AW, Singer J. Proton pump inhibitor utilization patterns in infants. J Pediatr Gastroenterol Nutr. 2007;45:421–7.
4. Chiesa C, Anania C, Pacifico L, Olivero G, Osborn JF. Helicobacter pylori therapy in children: a focus on proton pump inhibitors. Chemotherapy. 2011;57:85–93.
5. Gibbons TE, Gold BD. The use of proton pump inhibitors in children: a comprehensive review. Paediatr Drugs. 2003;5:25–40.
6. Turk H, Hauser B, Brecelj J, Vandenplas Y, Orel R. Effect of proton pump inhibition on acid, weakly acid and weakly alkaline gastro-esophageal reflux in children. World J Pediatr. 2013;9:36–41.
7. Hassall E, Kerr W, El-Serag HB. Characteristics of children receiving proton pump inhibitors continuously for up to 11 years duration. J Pediatr. 2007;150:262–7.
8. Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, et al. Therapy with gastric acidity inhibitors increases

the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics. 2006;117:e817–20.
9. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004;292:1955–60.
10. Pashankar DS, Israel DM. Gastric polyps and nodules in children receiving long-term omeprazole therapy. J Pediatr Gastroenterol Nutr. 2002;35:658–62.
11. Tytgat GN. Review article: long-term use of proton pump inhibitors in GORD—help or hindrance? Aliment Pharmacol Ther. 2001;15(Suppl 2):6–9.
12. DeVault KR, Castell DO, American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 2005;100:190–200.
13. Romano C, Chiaro A, Comito D, Loddo I, Ferrau V. Proton pump inhibitors in pediatrics: evaluation of efficacy in GERD therapy. Curr Clin Pharmacol. 2011;6:41–7.
14. van der Pol RJ, Smits MJ, van Wijk MP, Omari TI, Tabbers MM, Benninga MA. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. Pediatrics. 2011;127:925–35.
15. Kearns GL, Winter HS. Proton pump inhibitors in pediatrics: relevant pharmacokinetics and pharmacodynamics. J Pediatr Gastroenterol Nutr. 2003;37(Suppl 1):S52–9.
16. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors—emphasis on rabeprazole. Aliment Pharmacol Ther. 1999;13(Suppl 3):27–36.
17. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Cytochrome P450 3A: ontogeny and drug disposition. Clin Pharmacokinet. 1999;37:485–505.
18. Treluyer JM, Gueret G, Cheron G, Sonnier M, Cresteil T. Developmental expression of CYP2C and CYP2C-dependent activities in the human liver: in-vivo/in-vitro correlation and inducibility. Pharmacogenetics. 1997;7:441–52.
19. Omari T, Lundborg P, Sandstrom M, Bondarov P, Fjellman M, Haslam R, et al. Pharmacodynamics and systemic exposure of esomeprazole in preterm infants and term neonates with gastroesophageal reflux disease. J Pediatr. 2009;155:222–8.
20. Tammara BK, Sullivan JE, Adcock KG, Kierkus J, Giblin J, Rath N, et al. Randomized, open-label, multicentre pharmacokinetic studies of two dose levels of pantoprazole granules in infants and children aged 1 month through <6 years with gastro-oesophageal reflux disease. Clin Pharmacokinet. 2011;50:541–50.
21. Zhang W, Kukulka M, Witt G, Sutkowski-Markmann D, North J, Atkinson S. Age-dependent pharmacokinetics of lansoprazole in neonates and infants. Paediatr Drugs. 2008;10:265–74.
22. Kierkus J, Furmaga-Jablonska W, Sullivan JE, David ES, Stewart DL, Rath N, et al. Pharmacodynamics and safety of pantoprazole in neonates, preterm infants, and infants aged 1 through 11 months with a clinical diagnosis of gastroesophageal reflux disease. Dig Dis Sci. 2011;56:425–34.
23. Andersson T, Hassall E, Lundborg P, Shepherd R, Radke M, Marcon M, et al. Pharmacokinetics of orally administered omeprazole in children. International Pediatric Omeprazole Pharmacokinetic Group. Am J Gastroenterol. 2000;95:3101–6.
24. James L, Walson P, Lomax K, Kao R, Varughese S, Reyes J, et al. Pharmacokinetics and tolerability of rabeprazole sodium in subjects aged 12 to 16 years with gastroesophageal reflux disease: an open-label, single- and multiple-dose study. Clin Ther. 2007;29:2082–92.
25. Khoshoo V, Edell D, Thompson A, Rubin M. Are we overprescribing antireflux medications for infants with regurgitation? Pediatrics. 2007;120:946–9.
26. Omari T, Davidson G, Bondarov P, Naucler E, Nilsson C, Lundborg P. Pharmacokinetics and acid-suppressive effects of esomeprazole in infants 1–24 months old with symptoms of gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2007;45:530–7.
27. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr. 2009;154:514–20.
28. Springer M, Atkinson S, North J, Raanan M. Safety and pharmacodynamics of lansoprazole in patients with gastroesophageal reflux disease aged <1 year. Paediatr Drugs. 2008;10:255–63.
29. Winter H, Kum-Nji P, Mahomedy SH, Kierkus J, Hinz M, Li H, et al. Efficacy and safety of pantoprazole delayed-release granules for oral suspension in a placebo-controlled treatment-withdrawal study in infants 1–11 months old with symptomatic GERD. J Pediatr Gastroenterol Nutr. 2010;50:609–18.
30. Sherbaniuk RW, Wensel R, Trautman A, Grace M, Lentle B, Walker K, et al. Gastrin, gastric emptying, and gastroesophageal reflux after ranitidine. J Clin Gastroenterol. 1983;5:239–44.
31. Treem W, Hu P, Sloan S. Normal and proton pump inhibitor-mediated gastrin levels in infants 1 to 11 months old. J Pediatr Gastroenterol Nutr. 2013;57:520–6.
32. Moore DJ, Tao BS, Lines DR, Hirte C, Heddle ML, Davidson GP. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. J Pediatr. 2003;143:219–23.
33. Comer G, Baker R, Tsou V, et al. Randomized, double-blind clinical outcomes, safety, and tolerability study of pantoprazole delayed-release granules in children aged 1 to 5 years with endoscopically proven symptomatic gastroesophageal reflux disease (GERD). Gastroenterology. 2009;136:A-444 Abstract M1909.
34. Winter H, Gunasekaran T, Tolia V, et al. Esomeprazole for the treatment of GERD in infants ages 1–11 months. J Pediatr Gastroenterol Nutr. 2012;55(1):14–20.
35. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498–547.
36. Omari TI, Haslam RR, Lundborg P, Davidson GP. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. J Pediatr Gastroenterol Nutr. 2007;44:41–4.
37. Hussain S, Kierkus J, Hu P, Hoffman D, Lekich R, Sloan S, et al. Safety and efficacy of delayed release rabeprazole in 1 to 11 month-old infants with symptomatic GERD. J Pediatr Gastroenterol Nutr. 2014;58(2):233–43.
38. Orenstein SR, Shalaby TM, Cohn JF. Reflux symptoms in 100 normal infants: diagnostic validity of the Infant Gastroesophageal Reflux Questionnaire. Clin Pediatr (Phila). 1996;35:607–14.
39. Salvatore S, Vandenplas Y. Gastroesophageal reflux and cow milk allergy: is there a link? Pediatrics. 2002;110:972–84.
40. El-Serag HB, Aguirre TV, Davis S, Kuebeler M, Bhattacharyya A, Sampliner RE. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. Am J Gastroenterol. 2004;99:1877–83.
41. Sherman PM, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. Am J Gastroenterol. 2009;104:1278–95.
42. Bjornsson E, Abrahamsson H, Simren M, Mattsson N, Jensen C, Agerforz P, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther. 2006;24:945–54.

43. Fossmark R, Johnsen G, Johanessen E, Waldum HL. Rebound acid hypersecretion after long-term inhibition of gastric acid secretion. Aliment Pharmacol Ther. 2005;21:149–54.
44. Haddad I, Kierkus J, Tron E, Ulmer A, Hu P, Sloan S, et al. Efficacy and safety of rabeprazole in children (1–11 years) with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2013;57:798–807.
45. Haddad I, Kierkus J, Tron E, Ulmer A, Hu P, Silber S, et al. Maintenance of efficacy and safety of rabeprazole in children aged 1–11 years with endoscopically proven GERD. J Pediatr Gastroenterol Nutr. 2014;58(4):510–7.
46. Khoshoo V, Dhume P. Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 2008;46:352–4.
47. Gilger MA, Tolia V, Vandenplas Y. Safety and tolerability of esomeprazole in children with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2008;46(5):524–33.
48. Borrelli O, Rea P, de Bueno M, et al. Efficacy of combined administration of an alginate formulation (Gaviscon) and lansoprazole for children with gastroesophageal reflux disease. Ital J Pediatr. 2002;28:304–9.
49. Boccia G, Manguso F, Miele E, Buonavolonta R, Staiano A. Maintenance therapy for erosive esophagitis in children after healing by omeprazole: is it advisable? Am J Gastroenterol. 2007;102:1291–7.
50. Cucchiara S, Minella R, Iervolino C, Franco MT, Campanozzi A, Franceschi M, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Arch Dis Child. 1993;69:655–9.
51. Tolia V, Bishop PR, Tsou VM, Gremse D, Soffer EF, Comer GM, et al. Multicenter, randomized, double-blind study comparing 10, 20 and 40 mg pantoprazole in children (5–11 years) with symptomatic gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2006;42:384–91.
52. Gold BD, Gunasekaran T, Tolia V, Wetzler G, Conter H, Traxler B, et al. Safety and symptom improvement with esomeprazole in adolescents with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2007;45:520–9.
53. Tsou VM, Baker R, Book L, Hammo AH, Soffer EF, Wang W, et al. Multicenter, randomized, double-blind study comparing 20 and 40 mg of pantoprazole for symptom relief in adolescents (12 to 16 years of age) with gastroesophageal reflux disease (GERD). Clin Pediatr (Phila). 2006;45:741–9.