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**Widespread use of gastric acid inhibitors in infants: Are they needed? Are they safe?**

Mark S *et al.* Acid Suppression in Infants: Safety and Efficacy

**Mark Safe, Wei H, Steven T, Lee Sutton, Kei Lui, Usha Krishnan**

**Mark Safe, Lee Sutton, Usha Krishnan,**Department of Paediatric Gastroenterology, Sydney Children’s Hospital, Randwick NSW 2031, Australia

**Wei H Chan, Steven T Leach, Kei Lui, Usha Krishnan,** School of Women’s and Children’s health, University of New South Wales, Sydney NSW 2052, Australia

**Lee Sutton,** Department of Newborn Care, Royal Hospital for Women, Randwick NSW 2031, Australia

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**Correspondence to: Dr. Usha Krishnan,** Department of Paediatric Gastroenterology, Sydney Children’s Hospital, High Street, Randwick NSW 2031, Australia. usha.krishnan@sesiahs.health.nsw.gov.au

**Telephone:** +61-2-93821752

**Fax:** +61-2-93821753

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**Abstract**

Gastroesophageal reflux is a common phenomenon in infants, but the differentiation between gastroesophageal reflux and gastroesophageal reflux disease can be difficult. Symptoms are non-specific and there is increasing evidence that the majority of symptoms may not be acid-related. Despite this, gastric acid inhibitors such as proton pump inhibitors are widely and increasingly used, often without objective evidence or investigations to guide treatment. Several studies have shown that these medications are ineffective at treating symptoms associated with reflux in the absence of endoscopically proven oesophagitis. They have also questioned previously assumed links between reflux and other symptoms and complications in preterm and term infants. With a lack of evidence for efficacy, attention is now being turned to the potential risks of gastric acid suppression. Previously assumed safety of these medications is being challenged with evidence of potential side effects including GI and respiratory infections, bacterial overgrowth, adverse bone health, food allergy and drug interactions.

**Key words:** Gastroesophageal reflux; Infants; Proton pump inhibitors; Ranitidine; Safety; Adverse events

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**Core tip:** Gastroesophageal reflux is a common phenomenon in infants, but the differentiation between gastroesophageal reflux and gastroesophageal reflux disease can be difficult. Symptoms are non-specific and there is increasing evidence that the majority of symptoms may not be acid-related. Despite this, gastric acid inhibitors such as proton pump inhibitors are widely and increasingly used, often without objective evidence or investigations to guide treatment. Several studies have shown that these medications are ineffective at treating symptoms associated with reflux in the absence of endoscopically proven oesophagitis. They have also questioned previously assumed links between reflux and other symptoms and complications in preterm and term infants. With a lack of evidence for efficacy, attention is now being turned to the potential risks of gastric acid suppression. Previously assumed safety of these medications is being challenged with evidence of potential side effects including GI and respiratory infections, bacterial overgrowth, adverse bone health, food allergy and drug interactions.

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**INTRODUCTION**

Gastro-oesophageal reflux (GOR) is the physiologic process involving the passage of gastric contents into the oesophagus which is often accompanied by postprandial regurgitation or vomiting[1]. The term gastro-oesophageal reflux disease (GORD) applies to persistent reflux that causes troublesome symptoms and/or complications, and is therefore, considered pathologic[1]. This distinction remains a challenge in infant care.

Infants are physiologically predisposed to GOR because of their shorter intra-abdominal oesophagus, frequent liquid feeds that distend the stomach, and supine position[2]. Infants with GOR have been found to have frequent transient lower oesophageal sphincter relaxations, which are thought to be the pathophysiological basis of the condition. Fifty-percent of infants reportedly experience daily regurgitation in the first 3 mo of life, which resolve by 12-14 mo in most healthy infants[3]. The pathogenic mechanism leading infant GOR to develop into GORD is unclear, although decreased neural protective reflexes and delayed gastric emptying are thought to play a role[1].

Since infant GORD has been linked to significant clinical morbidity in some patients, including worsening lung disease, aspiration and oesophagitis, medical intervention is frequently sought[4]. Common and non-specific symptoms attributed to GOR are often considered troublesome enough to justify treatment, especially in the neonatal intensive care setting[5]. This has led to the widespread usage of gastric acid inhibitors (GAI), in the form of proton pump inhibitors (PPIs) and/or histamine-2 receptor antagonists (H2RAs) in infants, despite uncertainty as to their efficacy and risks. This report will review recent evidence on the suitability of PPIs as an effective therapy for GORD in symptomatic infants and their potential for short- and long-term side effects.

**GASTRIC ACID INHIBITOR USE IN INFANTS**

GAI use for infants with symptoms attributed to GORD has risen dramatically despite only very limited approval for their use in this age group[6,7]. From 2000 to 2003, there was a 4-fold increase in off-label PPI prescriptions in this age-group, despite less than 10% of patients being investigated for GORD by diagnostic procedure[8]. There has also been a concerning rise in the frequency of GAI use in preterm infants, despite the lack of published evidence regarding pharmacological management of GOR or the safety and efficacy of GAI in preterm infants. According to a survey of neonatologists across 77 secondary and tertiary NICUs, GORD is perceived to affect more than one-fifth of infants born before 34 weeks, and this perception may be leading to increased prescribing[9].

Symptoms described in infants with GORD include frequent regurgitation and vomiting, chronic cough, irritability, feeding resistance, failure to thrive, apnoea, bronchospasm and back-arching[2]. However, GORD diagnosis based on these symptoms is unreliable and non-specific. Regurgitation, irritability and vomiting thought to be secondary to GORD, are indistinguishable from the symptoms of food allergy, colic and other disorders[1]. Poor association between symptoms and pathologic acid exposure in oesophageal pH monitoring and histological scores, make symptoms unreliable in the diagnosis of GORD in infants[10]. GAI therapy in infants is largely extrapolated from studies of adults and older children, in whom symptoms are more reliably associated with acid exposure. In infants, significant recent data point to the possibility that the majority of symptoms are associated either with non-acid reflux or with no reflux at all[11]. In adults, there have been moves to even more potent acid suppression with the novel potassium competitive acid blockers such as vonoprazan. There is no safety data in children for this therapy, and considering that acid suppression has not been shown to affect symptoms in the majority of cases, there is likely to be very limited role for this drug.

Studies have also failed to find any association between GOR and cardiorespiratory events including apnoea, bradycardia, and oxygen desaturation in preterm infants[12,13]. Even so, two thirds of neonatologists have reported using GOR medications to treat apnoeas[14]. Overall, it has been widely recommended that GAI treatment in infants should be reserved for cases with evidence of pathological exposure to acid reflux episodes and/or oesophagitis[1]. Despite these recommendations, studies have found very poor adherence to guidelines and significant overtreatment with PPIs[15]. There is a concerning increase in the use of pharmacological intervention using acid suppression therapy using PPIs and H2RAs in preterm infants, with a presumed diagnosis of GORD based on symptoms alone in the absence of any objective measures for the diagnosis of GORD including pH and impedance monitoring or gastroscopy and biopsy[5]. Whilst there is no contemporary data outlining the relative frequency of H2RA and PPI use, the authors have observed a definite trend towards PPI as the predominant medication prescribed or acid suppression.

Although, GAIs have previously been considered to be well tolerated by infants, emerging evidence suggests potential harmful associations between the use of GAIs and the development of infection and atopic disease in murine, adult and limited paediatric studies[16,17]. GAIs serve to protect the mucosa from excessive acid production, however giving such aggressive acid suppression at such a young age without evidence of oesophagitis remains controversial. Acid suppression is thought to interfere with natural defences against gastric bacterial colonization[18], and also protein digestion to trigger allergic sensitization of dietary peptides[19]. There is also mounting evidence that children are being exposed to unnecessarily high doses of PPI with doses of 1mg/kg/day up to as high as 4mg/kg/day used in clinical practice. Recent randomised trials have shown that although there is a dose-dependant reduction in acid production, for the treatment of erosive esophagitis there is no significant difference in healing between 5mg/day and 10mg/day for children < 20 kg[20, 21].

**ACTION AND EFFICACY OF PPI**

PPIs bind irreversibly to the H+-K+-ATPase complex (“proton pump”) of gastric parietal cells to prevent the reuptake of extracellular potassium in exchange with intracellular hydrogen, thus inhibiting acid secretion[22]. Their use in infants has been extrapolated from numerous adult studies, for whom PPIs are superior in healing erosive oesophagitis and providing symptom relief compared with H2RAs, which are more effective than placebo[1]. PPIs have been found to maintain intragastric pH > 4 for prolonged periods and to inhibit meal-induced acid secretion.

However, PPIs have consistently failed to show efficacy in reducing infant GORD symptoms compared with placebo. Chen *et al*[23] reviewed four randomised control trials (RCTs) of PPIs in treating symptomatic GORD infants < 12 mo, conducted by pharmaceutical companies under formal requests by the Food and Drug Administration. The results of independent studies such as Moore *et al*[24] have corroborated with their results, which are summarised in Table 1[23-28]. Notably, Moore et al. enrolled infants with endoscopically confirmed GORD and found omeprazole significantly reduced the reflux index (percentage of total duration pH<4) in these infants compared with placebo, but irritability improved regardless of treatment[24]. In the most recent randomised controlled trial of PPI (Esomeprazole) for the treatment of symptomatic GORD, without endoscopy, all children were initially treated with PPI and then randomised to continuation of PPI or placebo[25]. It found no statistically significant difference in apparent treatment failure between the PPI or placebo group.

**SAFETY OF GASTRIC ACID INHIBITORS**

With any pharmacological agent, there is potential for side effects. Headache, diarrhoea, constipation and nausea are idiosyncratic effects of PPIs that occur in 14% of children[1]. Acute interstitial nephritis, a rare, idiosyncratic hypersensitivity reaction to medications including PPIs, has also been reported in observational adult studies[29]. Increased risk of infection, for example, Clostridium Difficile, is increasingly being recognised[30]. Side effects related to the direct inhibition of gastric acid and reflex hypergastrinaemia, immunosuppression and drug metabolism have also been suggested (Table 2).

***Bacterial overgrowth***

The human stomach has a median pH of 1.4, and a pH < 4 has a powerful bactericidal effect on ingested acid-sensitive bacteria[18]. PPIs often cause a gastric environment with pH > 4, inducing a state of hypochlorhydria which allows the overgrowth of bacteria in the stomach[18]. Recently, Kanno *et al*[31] observed the effect of gastric acid inhibition in altering lower-intestinal microflora in PPI treated rats and asymptomatic humans with achlorhydria. The authors showed a significant dose-dependent increase in Lactobacillus and Veillonella populations (bacteria of oropharyngeal origin) in both rats and humans and in rats, potent gastric acid inhibition also led to a marked and significant increase of intestinal bacteria, including the Bacteroides fragilis group[31]. Modern genomic techniques have confirmed these PPI-related changes through 16S sequencing[32]. These microbial changes are thought to be due to the lack of the gastric acid barrier allowing bacteria to enter the intestine and also the effect of impaired protein digestion providing nutrients to facilitate bacterial growth[31]. Links have previously been made between these and similar changes to intestinal microbiome and the pathogenesis of inflammatory and malignant conditions of the bowel[33].

***Risk of infections***

The pathogenic mechanism that allows enteric bacteria to cause gastrointestinal infections is multi-factorial. Gastric acid inhibition reduces the gastric microbiocidal barrier, delays gastric emptying, reduces gastric mucus viscosity thereby increasing the risk of bacterial translocation in addition to increasing the risk of colonisation by bacterial agents. Gastric acid inhibition also has an adverse effect on leukocyte function by decreasing adhesion to endothelial cells, reducing chemotactic response to bacterial proteins and inhibiting neutrophil phagocytosis by phagosome acidification[16]. This is potentially important in neonates and infants, who have immature humoral immunity[16]. A study on the numbers and type of bacteria in nasogastric tubes of patients receiving GAI demonstrated increased numbers of bacteria including Streptococcus, a known cause of community acquired pneumonia[34]. It is possible that the risk of pneumonia is increased as result of reflux aspiration of gastrointestinal contents into the lungs. PPIs may also directly inhibit the H+K+ATPase present in the respiratory tract, altering the pH of its seromucinous secretions[35].

***Adult studies***

A meta-analysis of 26 observational studies found a significant association between PPI/H2RA use and Clostridium difficile infections [pooled OR = 1.95, 95%CI: 1.48-2.58], and “other” enteric infections (Salmonella or Campylobactor) (OR = 2.55, 95%CI: 1.53-4.26)[36]. Salmonella, Campylobacter and the vegetative form of C. difficile are acid-sensitive bacteria but are able to survive with PPI-induced acid suppression[36]. Experimental studies have shown that pretreatment with gastric acid inhibitors in a mouse model prior to C. difficile inoculation resulted in similar rates of infection, toxin production and colon injury compared with a group of mice pretreated with ampicillin[36]. Spore germination was also favoured by high pH levels and the presence of potassium chloride. Blockage of potassium pumps in the stomach could potentially lead to increased potassium as the proton pumps exchange potassium for hydrogen ions.

In a systematic review, Bavishi and Dupont[18] found that while it was difficult to establish causation in some studies due to other contributing factors such as advanced age and hospital exposure, patients on PPIs demonstrated a greater-than 4-fold risk for recurrent C. difficile infection[37].

A meta-analysis by Eom *et al*[35] also found significant association between PPIs and pneumonia (adjusted OR = 1.27, 95%CI: 1.11-1.46), with an even greater risk for community-acquired pneumonia (OR = 1.34, 95%CI: 1.14-1.57). This risk of pneumonia was markedly higher within the first week of PPI use (OR = 3.95, 95%CI: 2.86-5.45) suggesting that patients who were already susceptible to pneumonia would become ill soon after PPI treatment. With a small number of studies investigating the relationship between PPIs and hospital-acquired pneumonia, only an increased risk of hospital-acquired pneumonia was observed with H2RA therapy[35].

***Paediatric studies***

 The few paediatric studies available have made similar conclusions. Notably, a prospective study of 93 paediatric patients (4-36 mo) with endoscopically diagnosed GORD, showed that children treated with either ranitidine or omeprazole for 8 weeks were 3.58 and 6.39 times more likely to develop acute gastroenteritis and community-acquired pneumonia respectively, compared with healthy children during the 4 month follow-up[17]. Comparing 4 months before and after enrolment, a significant increase in the incidence of acute gastroenteritis and pneumonia was found only in the treatment group, demonstrating that infection susceptibility could continue even after therapy cessation[17].

The results of safety studies on the use of gastric acid inhibiting drugs in infants, particularly in intensive care, where hospital-acquired pathogens are responsible for significant morbidity and mortality are concerning[38]. A case-control study of very low birth weight infants showed H2RA use was associated with higher rates of necrotizing enterocolitis (OR = 1.71, 95%CI: 1.34-2.19)[40]. Stoll *et al*[41] also observed an increased risk of sepsis and meningitis with H2RAs given at 2 wk of age as a secondary outcome of their RCT comparing dexamethasone exposure. Beck-Sague *et al*[42] also reported H2RAs as a significant risk factor for bloodstream infections (RR = 4.2) in level III neonatal intensive care, including Candida species; and the risk of candidemia (OR = 2.44) was shown again by Saiman *et al*[39]. Very few studies have explored the risk of infections in the preterm infant population, but of these, Guillet *et al*[40] showed H2RA use was associated with higher rates of necrotising enterocolitis (NEC) (OR = 1.71) in large cohort study of 11072 very low birth weight infants. H2RAs have also been found to be a significant risk factor for blood stream infections in a level III NICU[42], and candidemia[39]. The pathogenic mechanism of GAIs to cause infection is thought to be a result of reducing the gastric acid barrier against gastrointestinal tract colonisation with acid-sensitive bacteria such as Clostridium difficile[18]. Carrion and Egan[43] conducted a small prospective double-blind trial in 68 preterm infants (< 1250 g) supplemented with either HCl or water with feeds, and found that increased gastric bacterial colony counts were strongly correlated with gastric pH > 4 (*P* < 0.001), and acidification significantly reduced the incidences of NEC.

***Allergic sensitization***

Elevation of gastric pH also interferes with protein digestion, and it is hypothesised that normally digestible dietary peptides are preserved and recognised by the immune system as allergens[19]. Schöll *et al*[19] showed that omeprazole with hazelnut-extract treatment induced hazelnut-specific IgG1 in 3 of 5 mice (*P* = 0.754); and in the human study, 3.3% of patients receiving 3 months of H2RA/PPI treatment also developed de novo allergic sensitization, which was higher than the reported prevalence of all tree nut allergies in the general US population (0.2-0.7%). Schöll *et al*[44] also proposed that an allergic status induced in mothers had the potential to transfer (*via* placenta or breast milk) to the child. A study in pregnant mice demonstrated that increasing the gastric pH with sucralfate induced higher levels of codfish-specific IgG1 in mothers and offspring[44]. In offspring splenocytes, there was also a suppressed production of IFN- γ (Th1-cytokine), allowing the Th2-cytokine response to dominate (a phenotype predisposed to allergy); and T-regulatory cytokine IL-10, which regulates the allergic response[44]. A Swedish population register-based study found a significantly increased risk of developing childhood asthmas (51%), or any allergy (43%) in children exposed to PPIs/H2RAs in utero, irrespective of the drug type, trimester of exposure or maternal history of allergy[45].

**HYPERGASTRINAEMIA AND MUCOSA CHANGES**

Increasing gastric pH leads to hypergastrinemia, which has growth-promoting effects on several epithelial types[46]. Consequently, long-term PPI therapy is associated with parietal and enterochromaffin-like cell hyperplasia, as demonstrated by a RCT between esomeprazole treatment for 5 years compared with laparoscopic antireflux procedures for GORD[47]. Despite the proliferative drive of chronically elevated gastrin, no dysplastic changes were found.

Jalving *et al*[48] also found that PPI use > 1 year was associated with an increased risk of benign fundic gland polyps (OR = 2.8, 95%CI: 1.8-4.5), believed to arise from parietal cell protrusions and hyperplasia. One low-grade dysplastic polyp was found in a patient already predisposed with familial adenomatous polyposis, and did not appear to be PPI-related[48].

***Vitamin and mineral deficiencies***

By reducing gastric acidity, PPIs may interfere with the absorption of dietary protein-bound vitamin B12 and ionised calcium from dietary salts[22]. However, evidence of an effect of long-term PPI use in the elderly (over 65) on vitamin B12 has shown conflicting results. One case-control study (*n* = 53) found a 4.45 times increased risk for vitamin B12 deficiency in patients (> 12 mo of H2RAs/PPIs)[49]. However, a more recent cross-sectional study of 125 chronic (> 3 years) PPI users found no difference in serum vitamin B12 levels compared with controls[50].

PPIs have also been associated with an increased risk of fracture, as impaired calcium absorption is thought to cause a compensatory state of hyperparathyroidism to stimulate osteoclasts and bone resorption[51], but, there is also significant heterogeneity among these studies[52]. However, case-control studies have demonstrated significantly increased fracture risk in those with recent or current PPI use and at least one other risk factor for fracture[53,54].

During 2006-2012, there were 26 reported cases of hypomagnesaemia associated with PPIs in literature, with symptoms including electrocardiogram abnormalities and neuroexcitability, including tetanus and seizures, which resolved following withdrawal of PPI[52]. The mechanism of PPI-induced hypomagnesaemia is unknown, however, monitoring of serum magnesium levels has been recommended for susceptible patients, including patients using diuretics concurrently[55].

***Drug interactions***

In vitro studies have demonstrated a theoretical potential for PPIs and clopidogrel to interact through competitive binding at the cytochrome (CYP) 450 isoform CYP2C19, an enzyme involved in PPI metabolism[52]. Consequently, a significant reduction in the antiplatelet effect of clopidogrel has been reported. Although there have been no RCTs demonstrating increased cardiovascular risk, a recent propensity score analysis of a very large cohort showed an increased risk of myocardial infarction for adults taking PPI with an adjusted hazard ratio of 1.58[52].

**CONCLUSION**

This review highlights the issues regarding PPIs as treatment for infants with a presumed diagnosis of GORD based on symptomatology alone. For many clinicians, concern regarding the theoretical risk of tissue injury and secondary morbidities, seem to outweigh any concern for the risks of PPI use. Currently, several RCTs of PPIs have shown a consistent lack of efficacy in relieving ‘distressed’ GORD behaviours thought to be indicative of painful stimuli, suggesting they may have other underlying causes. Nonetheless, there is a need for more sizeable RCTs, standardised diagnostic procedures and better end-points in treatment in this population. Symptom assessments are clinically relevant but there is a lack of validated symptom-reported questionnaires for GORD in infants.

The safety of PPIs in infants also requires more prospective RCTs to remove the effect of confounders and bias. Irritable infants with uncomplicated GORD are hence recommended to continue lifestyle modifications, such as changing feeding techniques or formula composition, and avoid acid suppression. If PPIs are to be prescribed, only the minimal effective dose should be used, and should be weaned as soon as possible. There is no direct evidence to suggest increased safety of H2RA medication compared with PPI and in situations where acid suppression is indicated (*e.g.,* esophagitis) they have decreased potency. Attention should be paid to the substantial epidemiological evidence of increased infection risk with PPIs, and in the vulnerable population group of preterm infants, some authors suggest prophylactic measures.

**REFERENCES**

1 **Vandenplas Y**, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG. 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 [PMID: 19745761 DOI: 10.1097/MPG.0b013e3181b7f563]

2 **Blanco FC**, Davenport KP, Kane TD. Pediatric gastroesophageal reflux disease. *Surg Clin North Am* 2012; **92**: 541-558, viii [PMID: 22595708 DOI: 10.1016/j.suc.2012.03.009]

3 **Nelson SP**, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med* 1997; **151**: 569-572 [PMID: 9193240 DOI: 10.1001/archpedi.1997.02170430035007]

4 **Birch JL**, Newell SJ. Gastrooesophageal reflux disease in preterm infants: current management and diagnostic dilemmas. *Arch Dis Child Fetal Neonatal Ed* 2009; **94**: F379-F383 [PMID: 19307225 DOI: 10.1136/adc.2008.149112]

5 **Malcolm WF**, Gantz M, Martin RJ, Goldstein RF, Goldberg RN, Cotten CM. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. *Pediatrics* 2008; **121**: 22-27 [PMID: 18166553 DOI: 10.1542/peds.2007-0381]

6 **Sandström M**, Davidson G, Tolia V, Sullivan JE, Långström G, Lundborg P, Brown K. Phase I, multicenter, randomized, open-label study evaluating the pharmacokinetics and safety profile of repeated once-daily doses of intravenous esomeprazole in children 0 to 17 years of age. *Clin Ther* 2012; **34**: 1828-1838 [PMID: 22832034 DOI: 10.1016/j.clinthera.2012.06.028]

7 **Illueca M**, Alemayehu B, Shoetan N, Yang H. Proton pump inhibitor prescribing patterns in newborns and infants. *J Pediatr Pharmacol Ther* 2014; **19**: 283-287 [PMID: 25762873 DOI: 10.5863/1551-6776-19.4.283]

8 **Barron JJ**, Tan H, Spalding J, Bakst AW, Singer J. Proton pump inhibitor utilization patterns in infants. *J Pediatr Gastroenterol Nutr* 2007; **45**: 421-427 [PMID: 18030207 DOI: 10.1097/MPG.0b013e31812e0149]

9 **Dhillon AS**, Ewer AK. Diagnosis and management of gastro-oesophageal reflux in preterm infants in neonatal intensive care units. *Acta Paediatr* 2004; **93**: 88-93 [PMID: 14989446 DOI: 10.1080/08035250310007934]

10 **Salvatore S**, Hauser B, Vandemaele K, Novario R, Vandenplas Y. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? *J Pediatr Gastroenterol Nutr* 2005; **40**: 210-215 [PMID: 15699699 DOI: 10.1016/s8756-5005(08)70322-6]

11 **Orenstein SR**. Infant GERD: symptoms, reflux episodes & amp; reflux disease, acid & amp; non-acid refllux--implications for treatment with PPIs. *Curr Gastroenterol Rep* 2013; **15**: 353 [PMID: 24197743 DOI: 10.1007/s11894-013-0353-1]

12 **Di Fiore J**, Arko M, Herynk B, Martin R, Hibbs AM. Characterization of cardiorespiratory events following gastroesophageal reflux in preterm infants. *J Perinatol* 2010; **30**: 683-687 [PMID: 20220760 DOI: 10.1038/jp.2010.27]

13 **Smits MJ**, van Wijk MP, Langendam MW, Benninga MA, Tabbers MM. Association between gastroesophageal reflux and pathologic apneas in infants: a systematic review. *Neurogastroenterol Motil* 2014; **26**: 1527-1538 [PMID: 25080836 DOI: 10.1111/nmo.12405]

14 **Abu Jawdeh EG**, Martin RJ. Neonatal apnea and gastroesophageal reflux (GER): is there a problem? *Early Hum Dev* 2013; **89** Suppl 1: S14-S16 [PMID: 23809340 DOI: 10.1016/S0378-3782(13)70005-7]

15 **Quitadamo P**, Papadopoulou A, Wenzl T, Urbonas V, Kneepkens CM, Roman E, Orel R, Pavkov DJ, Dias JA, Vandenplas Y, Kostovski A, Miele E, Villani A, Staiano A. European pediatricians' approach to children with GER symptoms: survey of the implementation of 2009 NASPGHAN-ESPGHAN guidelines. *J Pediatr Gastroenterol Nutr* 2014; **58**: 505-509 [PMID: 24663035 DOI: 0.1097/MPG.0b013e3182a69912]

16 **Canani RB**, Terrin G. Gastric acidity inhibitors and the risk of intestinal infections. *Curr Opin Gastroenterol* 2010; **26**: 31-35 [PMID: 19907324 DOI: 10.1097/MOG.0b013e328333d781]

17 **Canani RB**, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, Passariello A, Manguso F, Morelli L, Guarino A. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006; **117**: e817-e820 [PMID: 16651285 DOI: 10.1542/peds.2005-1655]

18 **Bavishi C**, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. *Aliment Pharmacol Ther* 2011; **34**: 1269-1281 [PMID: 21999643 DOI: 10.1111/j.1365-2036.2011.04874.x]

19 **Schöll I**, Untersmayr E, Bakos N, Roth-Walter F, Gleiss A, Boltz-Nitulescu G, Scheiner O, Jensen-Jarolim E. Antiulcer drugs promote oral sensitization and hypersensitivity to hazelnut allergens in BALB/c mice and humans. *Am J Clin Nutr* 2005; **81**: 154-160 [PMID: 15640475]

20 **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 Pediatric Gastroenterol Nutr* 2015; **60**: S2-8 [DOI: 10.1097/01.mpg.0000469415.50085.f7]

21 **Tolia V,** Youssef NN, Gilger MA, Traxler B, Illueca M. Esomeprazole for the Treatment of Erosive Esophagitis in Children: An International, Multicenter, Randomized, Parallel-Group, Double-Blind (for Dose) Study. *J Pediatric Gastroenterol Nutr* 2015; **60**: S24-30 [DOI: 10.1097/01.mpg.0000469419.29000.94]

22 **Yang YX**, Metz DC. Safety of proton pump inhibitor exposure. *Gastroenterology* 2010; **139**: 1115-1127 [PMID: 20727892 DOI: 10.1053/j.gastro.2010.08.023]

23 **Chen IL**, Gao WY, Johnson AP, Niak A, Troiani J, Korvick J, Snow N, Estes K, Taylor A, Griebel D. Proton pump inhibitor use in infants: FDA reviewer experience. *J Pediatr Gastroenterol Nutr* 2012; **54**: 8-14 [PMID: 21946832 DOI: 10.1097/MPG.0b013e31823890b4]

24 **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**: 219-223 [PMID: 12970637 DOI: 10.1067/S0022-3476(03)00207-5]

25 **Winter H**, Gunasekaran T, Tolia V, Gottrand F, Barker PN, Illueca M. Esomeprazole for the Treatment of GERD in Infants Ages 1-11 Months. *J Pediatr Gastroenterol Nutr* 2015; **60** Suppl 1: S9-15 [PMID: 26422097 DOI: 10.1097/MPG.0b013e3182496b35]

26 **Omari T**, Davidson G, Bondarov P, Nauclér 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**: 530-537 [PMID: 18030229 DOI: 10.1097/MPG.0b013e31812e012f]

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**: 514-520.e4 [PMID: 19054529 DOI: 10.1016/j.jpeds.2008.09.054]

28 **Shakhnovich V**, Ward RM, Kearns GL. Failure of proton pump inhibitors to treat GERD in neonates and infants: a question of drug, diagnosis, or design. *Clin Pharmacol Ther* 2012; **92**: 388-392 [PMID: 22805424 DOI: 10.1038/clpt.2012.86]

29 **Sierra F,** Suarez M, Rey M, Vela MF. Systematic review: proton pump inhibitor-associated acute interstitial nephritis. *Alimentary Pharmacol Ther* 2007; **26**: 545-553 [PMID: 17661758 DOI: 10.1111/j.1365-2036.2007.03407.x]

30 **Turco R**, Martinelli M, Miele E, Roscetto E, Del Pezzo M, Greco L, Staiano A. Proton pump inhibitors as a risk factor for paediatric Clostridium difficile infection. *Aliment Pharmacol Ther* 2010; **31**: 754-759 [PMID: 20047577 DOI: 10.1111/j.1365-2036.2009.04229.x]

31 **Kanno T**, Matsuki T, Oka M, Utsunomiya H, Inada K, Magari H, Inoue I, Maekita T, Ueda K, Enomoto S, Iguchi M, Yanaoka K, Tamai H, Akimoto S, Nomoto K, Tanaka R, Ichinose M. Gastric acid reduction leads to an alteration in lower intestinal microflora. *Biochem Biophys Res Commun* 2009; **381**: 666-670 [PMID: 19248769 DOI: 10.1016/j.bbrc.2009.02.109]

32 **Rosen R**, Hu L, Amirault J, Khatwa U, Ward DV, Onderdonk A. 16S community profiling identifies proton pump inhibitor related differences in gastric, lung, and oropharyngeal microflora. *J Pediatr* 2015; **166**: 917-923 [PMID: 25661411 DOI: 10.1016/j.jpeds.2014.12.067]

33 **Gagnière J**, Raisch J, Veziant J, Barnich N, Bonnet R, Buc E, Bringer MA, Pezet D, Bonnet M. Gut microbiota imbalance and colorectal cancer. *World J Gastroenterol* 2016; **22**: 501-518 [PMID: 26811603 DOI: 10.3748/wjg.v22.i2.501]

34 **Vakil N**. Acid inhibition and infections outside the gastrointestinal tract. *Am J Gastroenterol* 2009; **104** Suppl 2: S17-S20 [PMID: 19262541 DOI: 10.1038/ajg.2009.47]

35 **Eom CS**, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ* 2011; **183**: 310-319 [PMID: 21173070 DOI: 10.1503/cmaj.092129]

36 **Leonard J**, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007; **102**: 2047-256; quiz 2057 [PMID: 17509031 DOI: 10.1111/j.1572-0241.2007.01275.x]

37 **Kim JW**, Lee KL, Jeong JB, Kim BG, Shin S, Kim JS, Jung HC, Song IS. Proton pump inhibitors as a risk factor for recurrence of Clostridium-difficile-associated diarrhea. *World J Gastroenterol* 2010; **16**: 3573-3577 [PMID: 20653067 DOI: 10.3748/wjg.v16.i28.3573]

38 **Saiman L**, Ludington E, Dawson JD, Patterson JE, Rangel-Frausto S, Wiblin RT, Blumberg HM, Pfaller M, Rinaldi M, Edwards JE, Wenzel RP, Jarvis W. Risk factors for Candida species colonization of neonatal intensive care unit patients. *Pediatr Infect Dis J* 2001; **20**: 1119-1124 [PMID: 11740316 DOI: 10.1097/00006454-200112000-00005]

39 **Saiman L**, Ludington E, Pfaller M, Rangel-Frausto S, Wiblin RT, Dawson J, Blumberg HM, Patterson JE, Rinaldi M, Edwards JE, Wenzel RP, Jarvis W. Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey study group. *Pediatr Infect Dis J* 2000; **19**: 319-324 [PMID: 10783022 DOI: 10.1097/00006454-200004000-00011]

40 **Guillet R**, Stoll BJ, Cotten CM, Gantz M, McDonald S, Poole WK, Phelps DL. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2006; **117**: e137-e142 [PMID: 16390920 DOI: 10.1542/peds.2005-1543]

41 **Stoll BJ**, Temprosa M, Tyson JE, Papile LA, Wright LL, Bauer CR, Donovan EF, Korones SB, Lemons JA, Fanaroff AA, Stevenson DK, Oh W, Ehrenkranz RA, Shankaran S, Verter J. Dexamethasone therapy increases infection in very low birth weight infants. *Pediatrics* 1999; **104**: e63 [PMID: 10545589 DOI: 10.1542/peds.104.5.e63]

42 **Beck-Sague CM**, Azimi P, Fonseca SN, Baltimore RS, Powell DA, Bland LA, Arduino MJ, McAllister SK, Huberman RS, Sinkowitz RL. Bloodstream infections in neonatal intensive care unit patients: results of a multicenter study. *Pediatr Infect Dis J* 1994; **13**: 1110-1116 [PMID: 7892080 DOI: 10.1097/00006454-199412000-00008]

43 **Carrion V**, Egan EA. Prevention of neonatal necrotizing enterocolitis. *J Pediatr Gastroenterol Nutr* 1990; **11**: 317-323 [PMID: 2246712 DOI: 10.1097/00005176-199010000-00006]

44 **Schöll I**, Ackermann U, Ozdemir C, Blümer N, Dicke T, Sel S, Sel S, Wegmann M, Szalai K, Knittelfelder R, Untersmayr E, Scheiner O, Garn H, Jensen-Jarolim E, Renz H. Anti-ulcer treatment during pregnancy induces food allergy in mouse mothers and a Th2-bias in their offspring. *FASEB J* 2007; **21**: 1264-1270 [PMID: 17227952 DOI: 10.1096/fj.06-7223com]

45 **Dehlink E**, Yen E, Leichtner AM, Hait EJ, Fiebiger E. First evidence of a possible association between gastric acid suppression during pregnancy and childhood asthma: a population-based register study. *Clin Exp Allergy* 2009; **39**: 246-253 [PMID: 19134022 DOI: 10.1111/j.1365-2222.2008.03125.x]

46 **Heidelbaugh JJ**, Metz DC, Yang YX. Proton pump inhibitors: are they overutilised in clinical practice and do they pose significant risk? *Int J Clin Pract* 2012; **66**: 582-591 [PMID: 22607510 DOI: 10.1111/j.1742-1241.2012.02921.x]

47 **Fiocca R**, Mastracci L, Attwood SE, Ell C, Galmiche JP, Hatlebakk J, Bärthel A, Långström G, Lind T, Lundell L. Gastric exocrine and endocrine cell morphology under prolonged acid inhibition therapy: results of a 5-year follow-up in the LOTUS trial. *Aliment Pharmacol Ther* 2012; **36**: 959-971 [PMID: 22998687 DOI: 10.1111/apt.12052]

48 **Jalving M**, Koornstra JJ, Wesseling J, Boezen HM, DE Jong S, Kleibeuker JH. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. *Aliment Pharmacol Ther* 2006; **24**: 1341-1348 [PMID: 17059515 DOI: 10.1111/j.1365-2036.2006.03127.x]

49 **Valuck RJ**, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. *J Clin Epidemiol* 2004; **57**: 422-428 [PMID: 15135846 DOI: 10.1016/j.jclinepi.2003.08.015]

50 **den Elzen WP**, Groeneveld Y, de Ruijter W, Souverijn JH, le Cessie S, Assendelft WJ, Gussekloo J. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. *Aliment Pharmacol Ther* 2008; **27**: 491-497 [PMID: 18194503]

51 **Insogna KL**. The effect of proton pump-inhibiting drugs on mineral metabolism. *Am J Gastroenterol* 2009; **104** Suppl 2: S2-S4 [PMID: 19262542]

52 **Chen J**, Yuan YC, Leontiadis GI, Howden CW. Recent safety concerns with proton pump inhibitors. *J Clin Gastroenterol* 2012; **46**: 93-114 [PMID: 22227731]

53 **Kaye JA**, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. *Pharmacotherapy* 2008; **28**: 951-959 [PMID: 18657011 DOI: 10.1592/phco.28.8.951]

54 **Corley DA**, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. *Gastroenterology* 2010; **139**: 93-101 [PMID: 20353792 DOI: 10.1053/j.gastro.2010.03.055]

55 **Danziger J**, William JH, Scott DJ, Lee J, Lehman LW, Mark RG, Howell MD, Celi LA, Mukamal KJ. Proton-pump inhibitor use is associated with low serum magnesium concentrations. *Kidney Int* 2013; **83**: 692-699 [PMID: 23325090]

56 **Shih CJ**, Chen YT, Ou SM, Li SY, Chen TJ, Wang SJ. Proton pump inhibitor use represents an independent risk factor for myocardial infarction. *Int J Cardiol* 2014; **177**: 292-297 [PMID: 25499395 DOI: 10.1016/j.ijcard.2014.09.036]

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##### Table 1 Summary randomised control trials examining proton pump inhibitors efficacy in reducing symptoms in infants with GORD

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Parameter | Esomeprazole | Lansoprazole | Pantoprazole | Omeprazole | Omeprazole (Independent)  | Esomeprazole |
| Control Group | Placebo | Placebo | Placebo | Dosing Range | Placebo  | Placebo |
| Blinding | Double | Double  | Double | Single | Double  | Double |
| Trial of Conservative Measures | No | Yes | Yes | Yes | Yes1 | No |
| Antacids allowed as rescue | Yes | No | Yes | Yes | No  | Yes |
| Open-label phase to identify PPI responders  | Yes (2 weeks) | No | Yes (4 weeks) | No | No  | Yes (2 weeks) |
| Randomised Withdrawal from PPI | Yes | No | Yes | No | Yes | Yes |
| Length of Randomised phase (wk) | 4 | 4 | 4 | 8 | 4  | 4 |
| Age in months | 1-12 | 1-12 | 1-12 | 0-243 | 3-12 | 1-11 |
| *N* | 40 | 81 | 50 | 35 | 30 | 80 |
| GORD Symptoms for clinical diagnosis | VomitingRegurgitationIrritabilitySupra-oesophageal disturbancesRespiratory DisturbanceFeeding Difficulty | Crying FussinessIrritability | VomitingRegurgitationSpitting upIrritabilityFussiness Feeding RefusalChokingGagging | Vomiting Regurgitation | 4Frequent spillingIrritability/Crying | Vomiting, regurgitation, irritability, cough, wheezing, stridor, labored breathing, resp symptoms triggered by feeding, food refusal, gagging, choking, hiccups for > 1 hour/d |
| Primary Endpoints | Time from randomisation to discontinuation because of symptom worsening perceived by parent or physician on symptom severity scale  | Proportion with ≤ 50% reduction in PGA of symptoms | Proportion of infants who withdrew due to the “lack of efficacy” including worsening of symptoms, and/or antacid use for 7 consecutive days and/or oesophagitis and/or physician judgements  | Change from baseline in daily symptoms based on PGA and parent perception  | Reflux index from baseline Change from baseline of parent-recorded 24 h crying and fussing time and visual analogue scores of parental impression of the intensity of irritability  | Time from randomization to discontinuation owing to symptom worsening in the double-blind phase |
| Primary end point efficacy result | Hazard Ratio= 0.69 (PPI/Placebo)95%CI: 0.35-1.35*P* = 0.275 | Responder rate:54% (44/81) PPI *vs* 54% (44/81) Placebo*P* = 1.000  | Responder rate: 12% PPI *vs* 11% Placebo *P* = 1.000 | Mean daily vomiting/regurgitation episodes decreased by 4.34 /d (0.5 mg/kg2.97/d – 1.0 mg/kg4.35/d – 1.5 mg/kg*P* > 0.50 in all group comparisons  | Reflux index -8.9 ± 5.6% PPI-1.9 ± 2.0% Placebo *P* < 0.001Cry/fuss times (min/24 h) 191 ± 120 (PPI)201 ± 100 (Placebo)*P* = 0.400Combined PPI and Placebo groups total cry fuss time2Baseline *vs* 2 wk *P* = 0.040Baseline *vs* 4 wk*P* = 0.008VA Score5.0 ± 3.1 (PPI)5.9 ± 2.1 (Placebo) *P* = 0.214 | Discontinuation rates owing to symptom worsening were 48.8% (20/41) for placebo-treated versus 38.5% (15/39) for esomeprazole-treated patients (hazard ratio 0.69; *P* = 0.28) |
| Limitations of studies | Small sample sizeSymptom-based diagnosisSubjective assessment | Small sample sizeSymptom-based diagnosisSubjective assessment | Small sample sizeSymptom-based diagnosisSubjective assessment | Single blinded Not placebo-controlledSmall sample sizeSymptom-based diagnosisSubjective assessment | Small sample size Subjective assessment | Small sample sizeSymptom-based diagnosisSubjective assessment |

##### 1All infants were given empirical pharmacologic treatment (excluding PPIs) including cisapride (87%), H2 Receptor antagonists (73%), antacid (67%) and thickening agent (20%); 2Significant decrease in cry-fuss time independent of treatment; 3 90% of patients were younger than 12 mo; 4 Entry into study required a reflux index of > 5% or endoscopic biopsy evidence of oesophagitis. Data adapted from Chen *et al*[23]; Moore *et al*[24]; Orenstein *et al*[27]; Shakhnovich *et al*[28]. PPI: Proton Pump Inhibitor; GORD: Gastro-oesophageal reflux disease; PGA: Physician Global Assessment; VA: Visual Analogue.

##### Table 2 Outline of the proposed side effects associated with proton pump inhibitors use, and the evidence supporting the association

|  |  |
| --- | --- |
| Potential side effects | Level of Evidence showing an association with PPI use  |
| Acute Interstitial Nephritis | Level III  |
| Bacterial overgrowth in the stomach, small and large intestine | Murine models |
| Bacterial enteric infectionsCausative agents: *Clostridium difficile**Salmonella* species*Campylobacter* species  | Level I |
| Pneumonia (Community-acquired) | Level I  |
| Necrotizing enterocolitis  | Level III1 |
| Blood stream infections, including candidemia  | Level III1 |
| Allergic sensitization in adults and in children with *in utero exposure* | Level III Study & Murine Models  |
| Parietal and Enterochromaffin-like cell hyperplasia | Level II  |
| Fundic gland polyps | Level III  |
| Vitamin B12 deficiency | Level III |
| Fractures (osteoporotic and non-osteoporotic) | Level III |
| Hypomagnesemia | Level IV and one level III study |
| Reduced Antiplatelet effect of Clopidogrel | Level II |
| Adverse Cardiovascular outcomes due to Clopidogrel interactions | Level III2  |

1 Only single reports showing an association with acid inhibition induced by H2RA treatment; 2 RCTs (level II) not shown an increase risk of adverse outcomes.