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MINIREVIEWS

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

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Abstract

Gastroesophageal reflux is a common phenomenon in infants, but the differentiation between gastro-esophageal 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. 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

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. 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 wk, 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 1 mg/kg per day up to as high as 4 mg/kg per 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 5 mg/d and 10 mg/d 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*[24] 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. 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

Table 1 Summary randomised control trials examining proton pump inhibitors efficacy in reducing symptoms in infants with gastro-oesophageal reflux disease

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	Yes[1]	No
Antacids allowed as rescue	Yes	No	Yes	Yes	No	Yes
Open-label phase to identify PPI responders	Yes (2 wk)	No	Yes (4 wk)	No	No	Yes (2 wk)
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	0-24[3]	3-12	1-11
n	40	81	50	35	30	80
GORD symptoms for clinical diagnosis	Vomiting; Regurgitation; Irritability; Supra-oesophageal disturbances; Respiratory Disturbance; Feeding difficulty	Crying; Fussiness; Irritability	Vomiting; Regurgitation; Spitting up; Irritability; Fussiness; Feeding Refusal; Choking; Gagging	Vomiting Regurgitation	[4]Frequent spilling Irritability/crying	Vomiting, regurgitation, irritability, cough, wheezing, stridor, labored breathing, resp symptoms triggered by feeding, food refusal, gagging, choking, hiccups for > 1 h/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	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/kg; 2.97/d – 1.0 mg/kg 4.35/d – 1.5 mg/kg; $P > 0.50$ in all group comparisons	Change from baseline of parent-recorded 24 h crying and fussing time and visual analogue scores of parental impression of the intensity of irritability Reflux index; -8.9% ± 5.6% PPI; -1.9% ± 2.0% Placebo $P < 0.001$ Cry/fuss times (min/24 h); 191 ± 120 (PPI); 201 ± 100 (Placebo) $P = 0.400$ Combined PPI and Placebo groups total cry fuss time[2] Baseline *vs* 2 wk $P = 0.040$ Baseline *vs* 4 wk $P = 0.008$ VA Score 5.0 ± 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 *vs* 38.5% (15/39) for esomeprazole-treated patients (hazard ratio 0.69; $P = 0.28$)
Limitations of studies	Small sample size Symptom-based diagnosis Subjective assessment	Small sample size; Symptom-based diagnosis; Subjective assessment	Small sample size Symptom-based diagnosis Subjective assessment	Single blinded; Not placebo-controlled; Small sample size; Symptom-based diagnosis; Subjective assessment	Small sample size; Subjective assessment	Small sample size; Symptom-based diagnosis; Subjective assessment

[1]All infants were given empirical pharmacologic treatment (excluding PPIs) including cisapride (87%), H2 receptor antagonists (73%), antacid (67%) and thickening agent (20%); [2]Significant decrease in cry-fuss time independent of treatment; [3]Ninty percent 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 infections	Level Ⅰ
Causative agents:	
Clostridium difficile	
Salmonella species	
Campylobacter species	
Pneumonia (Community-acquired)	Level Ⅰ
Necrotizing enterocolitis	Level Ⅲ[1]
Blood stream infections, including candidemia	Level Ⅲ[1]
Allergic sensitization in adults and in children with *in utero exposure*	Level Ⅲ Study and 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 Ⅲ[2]

[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.

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 wk 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 mo follow-up[17]. Comparing 4 mo 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)[39]. Stoll *et al*[40] 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*[41] 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*[42]. Very few studies have explored the risk of infections in the preterm infant population, but of these, Guillet *et al*[39] 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[41], 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 mo 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[55,56].

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, especially in the vulnerable population group of preterm infants.

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