Guide to Informed Decision-Making About PPIs: Research on Efficacy

The following research illustrates the efficacy of PPIs:

"**Omeprazole is effective in reducing esophageal acid exposure in premature infants** with pathological acid reflux on 24-h pH probe."

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

"PPIs play a pivotal role in the management of GERD but have not been found useful in infants with GER...**Unless there are warning features such as failure to thrive, haematemesis, abnormal posturing, choking/gagging or coughing while feeding, regurgitation** in infancy need not be investigated. In older children and adolescents with typical reflux symptoms, empirical PPI therapy is justified. For extra-oesophageal manifestations, a pH/impedance study and endoscopy to detect oesophagitis are the investigations of choice. **PPI is the mainstay of therapy in GERD**, but not in GER."

Poddar U. Gastroesophageal reflux disease (GERD) in children. *Paediatr Int Child Health*. 2019

"Many of the studies considered had significant methodological flaws, although based on available evidence the following statements can be made. **For infant GERD, ranitidine and omeprazole and probably lansoprazole are safe and effective medications, which promote symptomatic relief, and endoscopic and histological healing of esophagitis.** There is less evidence to support the use of domperidone or metoclopramide. More evidence is needed before other anti-reflux medications can be recommended. **The largest evidence base supports the early use of H(2) receptor antagonists or proton pump inhibitors."**

Tighe MP, Afzal NA, Bevan A, Beattie RM. Current pharmacological management of gastro-esophageal reflux in children: an evidence-based systematic review. *Paediatr Drugs*. 2009

"Omeprazole has been shown to be effective in the treatment of acid-related diseases. Marketed and extemporaneous formulations of **omeprazole have been administered to children aged 2 months to 18 years for the treatment of erosive esophagitis, gastric ulcer, duodenal ulcer, HP infection, and related conditions at dosages of 5 to 80 mg/d (0.2-3.5 mg/kg/d) for periods ranging from 14 days to 36 months with a low incidence of adverse effects.** The initial dose most consistently reported to heal esophagitis and provide relief of symptoms of GERD appears to be 1 mg/kg per day. In uncontrolled clinical trials and case reports to date, **omeprazole has been effective and well tolerated for the acute and chronic treatment of esophageal and peptic ulcer disease in children, particularly those who had failed to respond to previous treatment with histamine2-receptor antagonists.** Should future long-term, controlled clinical trials in children demonstrate safety and efficacy, this PPI is likely to find a place in the armamentarium of pediatric pharmacotherapy."

Zimmermann AE, Walters JK, Katona BG, Souney PE, Levine D. A review of omeprazole use in the treatment of acid-related disorders in children. *Clin Ther*. 2001

"Omeprazole therapy led to a marked decrease in symptoms, endoscopic and histologic signs of esophagitis, and intragastric acidity." (Study on infants)

Alliët P, Raes M, Bruneel E, Gillis P. Omeprazole in infants with cimetidine-resistant peptic esophagitis. *J Pediatr*. 1998

"Antisecretory reflux treatment improves extraesophageal reflux symptoms. **The efficacy of PPIs is superior to that of H(2) RAs** in these children.

Ummarino D, Miele E, Masi P, Tramontano A, Staiano A, Vandenplas Y. Impact of antisecretory treatment on respiratory symptoms of gastroesophageal reflux disease in children. *Dis Esophagus*. 2012

"Gastroesophageal reflux disease (GERD) has a prevalence of 10% to 20% in the pediatric population. The 24-hour pHmetry is still considered the "gold standard" for its correct diagnosis. **Omeprazole is the elective drug for a proper treatment. The comparison between the first and the second gastric pHmetry showed a statistically significant reduction in gastric acidity. This new presentation of omeprazole (OBA) with sodium bicarbonate and sodium alginate powder for oral suspension is capable of a significant and intense acid suppression, necessary for treatment of infants with GERD."**

Orsi M, Donato G, Busoni V, Naisberg G, Caruso N. Eficacia ácido supresora del omeprazol en polvo en lactantes con reflujo gastroesofágico. Estudio piloto [Gastric acid suppression of a new oral powder omeprazole suspension for infants with gastroesophageal reflux disease. A pilot study]. *Acta Gastroenterol Latinoam*. 2011

"Omeprazole is recognized as a safe and effective treatment of gastroesophageal reflux in older children, at an initial dosage of 0.7 mg x kg(-1) x day(-1). To our knowledge, no dose-finding studies have been carried out in children under 2 years of age. **Omeprazole is an effective treatment for gastroesophageal reflux in children younger than 2 years.** The majority respond to a dosage of 0.7 mg x kg(-1) x day(-1), but increased dosages up to 2.8 mg x kg(-1) x day(-1) may be required."

Bishop J, Furman M, Thomson M. Omeprazole for gastroesophageal reflux disease in the first 2 years of life: a dose-finding study with dual-channel pH monitoring. *J Pediatr Gastroenterol Nutr*. 2007

"Oral treatment with esomeprazole 0.25 mg/kg and 1 mg/kg was well tolerated and provided **dose-related acid suppression, dose-related exposure to esomeprazole, and decreased esophageal acid exposure in infants 1-24 months old with GERD."**

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

"Clinical symptoms in infants are mainly regurgitation and vomiting, which usually disappear between 1 and 3 years of age. Symptoms in children are similar to those in adults. **Treatment in children depends on age and GORD severity.** Prokinetics either have unproven efficacy (metoclopramide, domperidone) or have been withdrawn (cisapride). Chronic antacid therapy is not recommended. **In moderate to severe GORD, histamine-2-receptor antagonists and particularly proton pump inhibitors (PPIs) are effective, especially when oesophagitis is present. PPIs, in particular omeprazole and lansoprazole, have proven efficacy in infants and children."**

Cezard JP. Managing gastro-oesophageal reflux disease in children. *Digestion*. 2004

"Clinical manifestations of GOR in children range from regurgitation, food refusal, irritability, failure to thrive, hematemesis, wheezing and aspiration pneumonia, apnoea and apparent life threatening events in infants to clinically silent reflux...H2-receptor antagonists are indicated in GOR complicated by esophagitis. Ranitidine is regarded to be more potent. Cimetidine has additional spectrum of adverse effects and sufficient information is not available on famotidine. **Omeprazole has been shown to be effective in treating GOR-esophagitis resistant to H2 antagonist therapy even in high risk patients."**

Sandhu BK, Sawczenko A. Gastroesophageal reflux in children. *Indian J Pediatr*. 1999

"Following failure of conventional therapy for reflux oesophagitis, 15 children were treated with omeprazole 20 mg daily for a period of up to three months initially. **Treatment resulted in a marked symptomatic improvement as measured by incidence of pain, vomiting, dysphagia and haematemesis."**

Martin PB, Imong SM, Krischer J, Noblett HR, Sandhu BK. The use of omeprazole for resistant oesophagitis in children. *Eur J Pediatr Surg*. 1996

"Patients were initially given omeprazole at 10 to 20 mg; **the dose was titrated upward until results of a subsequent 24-hour intraesophageal pH study was normal. Symptoms and signs abated and evidence of esophagitis diminished in all patients.** Omeprazole was given for periods of 5.5 to 26 months (mean, 12.2 months). The effective total dose was 20 to 40 mg (0.7 to 3.3 mg/kg) in 11 patients, 10 mg (0.7 mg/kg) in 1 patient, and 60 mg (1.9 to 2.4 mg/kg) in 3 patients. The dosage range was 0.7 to 3.3 to mg/kg per day (mean, 1.9 mg/kg)...**We found omeprazole to be highly effective in this group of patients with severe esophagitis refractory to other measures."**

Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *J Pediatr*. 1993

"The mean number of **acid reflux episodes of >5 minutes duration decreased from 6 at baseline to 3 and 2 with esomeprazole** 0.25 mg/kg and 1 mg/kg, respectively."

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*. 2015

"In children ages 1 to 11 years with endoscopically proven GERD, esomeprazole (at daily doses of 5, 10, or 20 mg) was generally well tolerated. **The frequency and severity of GERD-related symptoms were significantly reduced during the active treatment period."**

Gilger MA, Tolia V, Vandenplas Y, Youssef NN, Traxler B, Illueca M. Safety and Tolerability of Esomeprazole in Children With Gastroesophageal Reflux Disease. *J Pediatr Gastroenterol Nutr*. 2015

"Under PPI, an improvement of pain-related symptoms could be shown. The decrease of acid exposure went along with an increase of non-acidic refluxes resulting in almost constant total reflux numbers. This finding is interpreted as main reason for some persisting symptoms despite adequate PPI dosage. Concluding from our data **PPI therapy should only be indicated in case of pain**, but has no effect in case of vomiting or recurrent respiratory symptoms."

Castellani C, Huber-Zeyringer A, Bachmaier G, Saxena AK, Höllwarth ME. Proton pump inhibitors for reflux therapy in infants: effectiveness determined by impedance pH monitoring. *Pediatr Surg Int*. 2014

"Our results suggest that exposition time to **GER without treatment with PPI is related to Barrett's oesophagus** development in childhood."

Sanchís Blanco G, Ibáñez Pradas V, Couselo Jerez M, Fonseca Martín R, Vila Carbó JJ, García-Sala Viguer C. Factores de riesgo del esófago de Barrett en niñios: estudio caso-control [Risk factors for Barrett's oesophagus in children: a case-control study]. *Cir Pediatr*. 2013

"Patients with EoE treated with PPIs show an improvement in symptoms and z-scores despite persistent eosinophilic inflammation. **PPI treatment may be useful maintenance therapy in children with EoE."**

Levine J, Lai J, Edelman M, Schuval SJ. Conservative long-term treatment of children with eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2012

"GER disease (GERD) occurs when reflux of the gastric contents causes symptoms that **affect the quality of life or pathologic complications, such as failure to thrive, feeding or sleeping problems, chronic respiratory disorders, esophagitis, hematemesis, apnea, and apparent life-threatening events.** Irritability coupled with back arching in infants is thought to be a non-verbal equivalent of heartburn in older children. Other causes of irritability, including cow's milk protein allergy, neurologic disorders, constipation and infection, should be ruled out. The presentation of cow's milk protein allergy overlaps with GERD, and both conditions may co-exist in 42-58 % of infants. In these infants, symptoms decrease significantly within 2-4 weeks after elimination of cow's milk protein from the diet. For non-complicated reflux, no intervention is required for most infants. Effective parental reassurance and education regarding regurgitation and lifestyle changes are usually sufficient to manage infant reflux. **Sandifer syndrome, apnea and apparent life-threatening events are the extraesophageal manifestations of GERD in infants**...there is insufficient evidence to justify the routine use of prokinetic agents. **Esomeprazole (Nexium) is now approved in the US for short-term treatment of GERD with erosive esophagitis in infants aged from 1 to 12 months.** Although Nissen fundoplication is now well established as a treatment option in selected cases of GERD in children, its role in neonates and young infants is unclear and is only reserved for selective infants who did not respond to medical therapy and have life-threatening complications of GERD."

Czinn SJ, Blanchard S. Gastroesophageal reflux disease in neonates and infants : when and how to treat. *Paediatr Drugs*. 2013

"In children 1 to 11 years of age, **lansoprazole is efficacious in healing EE [erosive esophagitis] and in relieving GERD-related symptoms."**

Tolia V, Ferry G, Gunasekaran T, Huang B, Keith R, Book L. Efficacy of lansoprazole in the treatment of gastroesophageal reflux disease in children. *J Pediatr Gastroenterol Nutr*. 2002

"Our experience suggests that in infants with congenital diaphragmatic eventration who present with respiratory distress gastro-oesophageal reflux should be suspected, and **PPI therapy should be started before planning surgery."**

Zicari AM, Tancredi G, Rugiano A, et al. An infant with diaphragmatic eventration and respiratory distress. *J Biol Regul Homeost Agents*. 2010

"GER disease (GERD) refers to the appearance of troublesome symptoms or complications (erosive esophagitis, ulceration, Barrett's esophagus) and may warrant acid suppression. **Proton Pump Inhibitors (PPIs) are the most effective pharmacologic agents available for the treatment of children with GERD.** In the pediatric practice only omeprazole, lansoprazole and esomeprazole are available over the first year of life. The empiric use in infants with nonspecific symptoms (excessive crying, regurgitation, feeding refusal, chronic cough) is frequent without randomized controlled study."

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

The following research questions the effectiveness of PPIs in infants. You can see my commentary on each quote underneath.

"...esomeprazole in 26 preterm infants and term neonates with symptoms of gastroesophageal reflux and pathologic acid exposure. **Enrolled patients received oral esomeprazole 0.5 mg/kg once daily for 7 days. There were no significant differences from baseline to day 7 of therapy** in the frequency of bolus reflux, consistency of bolus reflux (liquid, mixed, or gas), extent of bolus reflux, or bolus clearance time. The number of gastroesophageal reflux symptoms recorded over 24 hours was lower on therapy. In preterm infants and term neonates esomeprazole produces no change in bolus reflux characteristics despite significant acid suppression."

[Compare proper dosing with the dose that these infants were given, 0.5 mg/kg ONE time per day. Proper dosing for under three months is 1.5 mg/kg THREE times per day. This study is stating that the esomeprazole reduced the amount of acid, but not the amount of spit-up. This is to be expected! Spit-up is normal. Pain from acidic spit-up is not, nor should it be acceptable.]

Omari T, Lundborg P, Sandström M, et al. Pharmacodynamics and systemic exposure of esomeprazole in preterm infants and term neonates with gastroesophageal reflux disease. *J Pediatr*. 2009

"Eight studies demonstrated that both proton pump inhibitors and histamine H2 receptor antagonists were effective against typical manifestations of gastroesophageal reflux disease, and that there was no evidence of benefit in combining the latter to the former or in routinely prescribing long-term maintenance treatments. **Another study demonstrated that omeprazole performed better than ranitidine for the treatment of extraesophageal reflux manifestations. Ten studies failed to demonstrate significant benefits of proton pump inhibitors or histamine H2 receptor antagonists** for the treatment of unspecific manifestations attributed to gastroesophageal reflux in infants. **Proton pump inhibitors or histamine H2 receptor antagonists may be used to treat children with gastroesophageal reflux disease"**

[This was a review of multiple studies and the data was all over the place. Some showed effectiveness, while others did not. There were many inconsistencies in the amount of medication given as well as the frequency.]

Mattos ÂZ, Marchese GM, Fonseca BB, Kupski C, Machado MB. ANTISECRETORY TREATMENT FOR PEDIATRIC GASTROESOPHAGEAL REFLUX DISEASE - A SYSTEMATIC REVIEW. *Arq Gastroenterol*. 2017

"Moderate evidence was found to support the use of PPIs, along with some evidence to support the use of H_2 antagonists in older children with GORD, based on improvement in symptom scores, pH indices and endoscopic/histological appearances. However, lack of independent placebo-controlled and head-to-head trials makes conclusions as to relative efficacy difficult to determine. Further RCTs are recommended. No robust RCT evidence is available to support the use of domperidone, and further studies on prokinetics are recommended, including assessments of erythromycin. Pharmacological treatment of infants with reflux symptoms is problematic, as many infants have GOR, and little correlation has been noted between reported symptoms and endoscopic and pH findings. **Better evidence has been found to support the use of PPIs in infants with GORD, but heterogeneity in outcomes and in study design impairs interpretation of placebo-controlled data regarding efficacy...Studies of omeprazole and lansoprazole in infants with functional GOR have demonstrated variable benefit, probably because of differences in inclusion criteria.** No robust RCT evidence has been found regarding treatment of preterm babies with GOR/GORD or children with neurodisabilities. Initiation of RCTs with common endpoints is recommended, given the frequency of treatment and the use of multiple antireflux agents in these children."

[The article specifically states that there just isn't a wide enough variety of research available.]

Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-oesophageal reflux. *Cochrane Database Syst Rev*. 2014;(11):CD008550. Published 2014 Nov 24.

"Clinical trials reveal that PPI therapy is not an effective treatment for common infant GERD-associated symptoms. Evidence supporting safety of PPI use in infants is conflicting, and more large-scale, randomized, placebo-controlled trials are necessary to better establish the role of PPIs in infant GERD."

[Again, more research is needed!]

Higginbotham TW. Effectiveness and safety of proton pump inhibitors in infantile gastroesophageal reflux disease. *Ann Pharmacother*. 2010

"In only 3 of these was the efficacy of omeprazole studied in children under the age of 1 year. These studies showed that there was an effect on the acidity of the stomach, but not on symptoms. Although many side effects may occur during the use of omeprazole, few suspected side effects were reported to the Lareb Netherlands pharmacovigilance centre. It is uncertain whether acid reflux is the cause of crying in babies and, if reflux is suspected, whether omeprazole is the preferred treatment."

[It seems the main symptom of reflux that was examined here is crying. While crying is one symptom of reflux, there are many others associated with pain such as arching back, painful burping, poor sleep, etc. The discussion even admits that there was some reduction of acid on a PPI, even though crying may not have been significantly reduced.]

Blokpoel RG, Broos N, de Jong-van den Berg LT, de Vries TW. Waarde omeprazol bij huilende zuigelingen beperkt [Omeprazole of limited value in crying babies]. *Ned Tijdschr Geneeskd*. 2010

"...weight-adjusted doses of esomeprazole **(2.5-10 mg) once daily** for 2 weeks. Infants with symptom improvement were randomized to esomeprazole (**weight-adjusted doses [2.5-10 mg]**) or placebo for 4 weeks. During this phase, discontinuation rates owing to symptom worsening were 48.8% (20/41) for placebo-treated versus 38.5% (15/39) for esomeprazole-treated patients."

[Patients got worse and stopped the trial almost equally on the placebo vs the esomeprazole. This could be attributed to under-dosing causing a continuous acid battle.]

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

"In this randomized, double-blind, placebo-controlled multicenter study, neonates (premature to 1 month corrected age; n = 52) with signs and symptoms of GERD received esomeprazole **0.5 mg/kg or placebo once daily** for up to 14 days. There were no significant differences between the esomeprazole and placebo groups in the percentage change from baseline in the total number of GERD-related signs and symptoms. Signs and symptoms of GERD traditionally attributed to acidic reflux in neonates were not significantly altered by esomeprazole treatment. Esomeprazole was well tolerated and reduced esophageal acid exposure and the number of acidic reflux events in neonates."

[Compare proper dosing with the dose that these infants were given, 0.5 mg/kg ONE time per day. Proper dosing for under three months is 1.5 mg/kg THREE times per day. This study is stating that the esomeprazole reduced the amount of acid exposure, not fussiness.]

Davidson G, Wenzl TG, Thomson M, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. *J Pediatr*. 2013