Summary of Studies for GER in Neonates for Prokinetics, H2 Blockers and PPIs

PICOT Question:
In infants in the ICN with suspected gastroesophageal reflux does treatment with erythromycin, H2 Blockers or proton pump inhibitors improve symptoms?

Clinical bottom line based on literature appraisal below:
We think pharmacological treatment should be reserved for infants in whom there is concern for GER causing harmful sequelae. Medications have not been shown to be effective in improving symptoms and may be associated with adverse effects, and so should be reserved for infants who fail non-pharmacologic measures.

Some evidence weakly supports the use of prokinetic agents (specifically Erythromycin) in treatment for feeding intolerance, which may indirectly decrease GER. Acid suppression agents (H2 blockers and Proton Pump Inhibitors) increase gastric pH, but have not been shown to reduce the symptoms of GER.

Potential adverse effects from medications causing gastric acid suppression have been noted, including a possible link to necrotizing enterocolitis, altered gastric colonization, and increased pneumonia.

Search strategy implemented:
"Infant"[Mesh] OR "Infant, Premature"[Mesh]) AND "Gastroesophageal Reflux/therapy"[Mesh]

Search outcome:
Seven articles reviewed; two randomized control trials, one randomized crossover design, one case study series, one expert opinion, one retrospective observational study, one case series/individual case control study.
<table>
<thead>
<tr>
<th>Author, date, country, and industry of funding</th>
<th>Patient Group</th>
<th>Level of Evidence (Oxford) / Strength of Evidence (GRADE)</th>
<th>Research design</th>
<th>Significant results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuntnarumit P, Kiatchoosakun P, Tantiprapa W et al. Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. J Pediatr 2006;148:600-6005.</td>
<td>All gestational age &lt;35 weeks (42/46 were &lt;32 wks), birth weight &lt;1800g, postnatal age at least 5 days</td>
<td>1b: RCT with narrow confidence interval (95%)- trial also met power</td>
<td>Randomized, double-blinded, placebo-controlled trial</td>
<td>Time to full feedings was significantly shorter in the EM group (p&lt;0.001) Breast milk feeding vs. formula didn’t show difference Same effect was seen when ages were divided (&lt;32wks vs. ≥32 wks) No significant difference in ae’s (cholestatic jaundice, sepsis, NEC and mortality) Power was only met for efficacy, not AE’s No incidence of hypertrophic pyloric stenosis or cardiac arrhythmias</td>
<td>Study for FEEDING INTOLERANCE 7 day trial for Feeding intolerance, GER would be treated much longer Exposure &gt;14 days increases incidence of hypertrophic pyloric stenosis by 10 fold Mild degree of feeding intolerance used in study, may illicit a better response due to more mature GI tract MMC activity of GI doesn’t occur until 32 weeks GA, and is not mature until 35 wks</td>
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<tr>
<td>Ng SCY, Gomez JM, Rajadurai VS et al. Establishing Enteral Feeding in Preterm Infants with Feeding Intolerance: A Randomized Controlled Study of Low-dose Erythromycin. Journal of Pediatric Gastroenterology and Nutrition. Nov 2003;37,554-558.</td>
<td>24 patients (met 80% power) Preterm infants (birth weight less than or equal to 1500gm) Gestational age 27.5 ± 2.9 weeks (placebo) and 27.1 ± 1.9 weeks (erythromycin)</td>
<td>2b (RCT with no CI which makes it a low quality RCT)- did meet power and express p values</td>
<td>Prospective, double-blind, randomized controlled trial.</td>
<td>Trial conducted distal esophageal pH studies on infants to assess treatment of GER, “GER decreased in both groups over time and thus seems likely to be an effect of maturation rather than a result of erythromycin therapy” “oral erythromycin at low doses did NOT reduce the time taken to attain full enteral feeds” AE: more infants in placebo group developed cholestatic jaundice (p=0.113), no infants developed dysrhythmias, no increase in hypertrophic pyloric stenosis</td>
<td>Treatment of FEEDING INTOLERANCE. Heterogeneity of demographic characteristics between groups Erythromycin group weighed less and had more IUGR</td>
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Reviewed/Revised: 10/08; 2/09, 6/107/7/2010
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omari, T.I., Haslam, R.R., Lundborg, P. &amp; Davidson G.P. (2007)</td>
<td>Randomized, double blinded, placebo controlled, crossover design</td>
<td>Omeprazole reduced gastric acidity. There was no change in the symptomatic events of GER</td>
<td>Study has small sample size. The criterion for inclusion is somewhat inconclusive. Power is not stated. Duration of the trial is questionable.</td>
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<tr>
<td>10 infants; mean post menstrual age of 36.1 (+/-) 0.7 weeks with symptoms suggestive of GER</td>
<td>2b</td>
<td></td>
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<tr>
<td>Salvatore, S., Hauser, B., Salvatoni, A. &amp; Vandenplas, Y. (2006)</td>
<td>Case Study Series</td>
<td>Ranitidine decreased gastric acidity and was beneficial in treating acid related esophagitis. “the impact of ranitidine on the duration gastric pH is &gt;4.0 with persistent GOR [oesophageal] symptoms is limited to none.”</td>
<td>No control group. Absence of standardization.</td>
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<tr>
<td>103 infants; mean age 3.3 (+/-) 1.8 months with persisting suspected GER</td>
<td>4</td>
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<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Study type</th>
<th>Participants</th>
<th>Study design</th>
<th>Key findings</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandenplas, Y., Salvatore, S., &amp; Hauser B. (2005).</td>
<td>The diagnosis and management of gastro-oesophageal reflux in infants. <em>Early Human Development</em>. 81(12):1011-24</td>
<td>Infants</td>
<td>5</td>
<td>Expert opinion based on physiology or other lab research</td>
<td>Ranitidine is useful in esophagitis. Ranitidine has not been shown to resolve clinical symptoms of GER. Omeprazole is very useful in acid suppression leading to improvement in cases of acid related esophagitis. There are insufficient studies of PPIs in the patient population.</td>
<td>“Take it for what it’s worth”. Article is based on expert opinion. Broad scope and good overview of current practices and recommendations on the basis of literature review and study analysis.</td>
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<tr>
<td>Fontana, M., Tornaghi, R, Petrillo, M., Lora, E., Pooro, G.B. &amp; Principi, N. (1993).</td>
<td>Ranitidine treatment in newborn 30 infants with bloody vomiting and endoscopically proved esophageal bleeding. Mean gestational</td>
<td>4 /3b</td>
<td>Case series study / Individual Case Control</td>
<td>Gastric pH increased with ranitidine usage. Correlation between ranitidine usage and increased prolactin was not found. Healing of esophagitis was seen in the ranitidine group</td>
<td>This study addresses gastric pH and how it is lowered but does not address GER.</td>
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infants: Effects on gastric acidity and serum prolactin levels. *Journal of Pediatric Gastroenterology and Nutrition, 16*, 406

- age 39.5 (+/-) 1.6 weeks.

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References


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