

**Gastroesophageal Reflux**  
**East Bay Newborn Specialists Guideline**  
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## **Background**

Gastroesophageal reflux is a common occurrence in the neonatal intensive care unit, occurring in up to 85% of premature newborns<sup>1</sup>. In adult populations, the implications of gastroesophageal reflux can be significant, with acidic refluxate causing significant symptomatology, and predisposing to the development of esophageal malignancy. This has led to the term “gastroesophageal reflux disease” or GERD. Neonatal reflux differs from adult reflux in many ways. These differences have significant implications for reflux management in the population we care for. There has been conflicting data linking reflux to various morbidities including most notably apnea of prematurity. This has led to aggressive management of reflux using similar medications used to treat adult GERD, with 25% of premature neonates in 2008 being treated with reflux medications.

This discussion and the supporting literature apply to structurally and neurologically normal neonates. That being said, the pharmacologic literature may be even more concerning in such vulnerable infants.

### ***Reflux:***

Simply defined, reflux is the retrograde movement of gastric contents into the esophagus. Using this definition all babies who spit up have reflux. With this broad definition, it is clear that reflux is a common entity, and should be regarded as such rather than as pathology. The term GERD implies a disease state, and should be avoided in reference to premature infants.

The physiologic immaturity of the neonate has significant implications for reflux:

- The lower esophageal sphincter is poorly developed in neonates, even more so in premature infants, and so offers little resistance.
- Neonates spend most of their time in a recumbent position.
- Neonates consume frequent liquid feedings, increasing the potential for reflux.
- Gastric pH is extremely variable in neonates.
- Post-prandial reflux events tend to be non-acidic.

### ***Apnea and Reflux:***

As a result of their immaturity, premature infants are at risk for both reflux events, and for apnea. Laryngeal reflexes trigger epiglottic closure in response to reflux. Animal studies have shown a disturbance in respiratory control with fluid in the larynx. Such data present an attractive link between reflux and apnea. Several articles in the late 70s linked reflux with significant pathology ranging from apnea to “near miss SIDS” leading to an aggressive physiologic and pharmacologic approach to the management of reflux in the belief that apnea could be improved or prevented.

Much work has been done to elucidate the nature of the relationship between apnea and reflux and although there are still many questions, it appears clear that reflux does not cause apnea. Concurrent tracings of diaphragmatic EMG and lower esophageal sphincter tone show apnea preceding a decrease in lower esophageal sphincter tone, which returned to baseline with return of respiratory efforts. This makes sense when considering the immature nature of the lower esophageal sphincter, and the role of diaphragmatic tone in LES function. Similar data from Omari and colleagues shows a fall in esophageal sphincter tone following an

apneic episode. A study comparing frequency of apnea to frequency of reflux events showed no relationship between the two. A large study evaluating over 2000 apneic episodes in premature infants showed the vast majority of apneas occurring unrelated to reflux, and when temporally related apnea commonly preceded reflux. A separate study of term infants being evaluated for ALTE showed only half of infants with apnea to have reflux. Of those infants with apnea and reflux, < 20% of apneas were temporally related to reflux episodes with apnea preceding reflux over 90% of the time.

### ***Diagnostic Studies:***

Several studies are available to document reflux episodes including pH probe studies, multichannel intraluminal impedance, UGI and gastric emptying studies. There are significant limitations to each, and all are invasive. Little is contributed by these studies, beyond the clinical report of infant spitting. As episodes of post-prandial reflux are not acidic, a pH probe study is difficult to interpret clinically. Multichannel intraluminal impedance is extremely sensitive to liquid, regardless of pH, and can give information for height of refluxate, but in the absence of normals is extremely difficult to interpret. UGI studies are helpful to rule out anatomic abnormalities, but have little role with regard to reflux. A child with history of clinical reflux has reflux even in the face of a negative study. Gastric emptying studies are potentially helpful in children with dysmotility, but again, are not warranted in the premature infant with reflux.

Given the limited additional value contributed by any of these studies, and difficulty with their interpretation, bedside observation, and nursing reports are adequate for the diagnosis of reflux.

## **Non-pharmacologic Therapy**

### ***Positioning:***

Logically, as an infant's recumbent position predisposes to reflux, alternate positioning may decrease the tendency to reflux. The anatomical orientation of the lower esophageal sphincter is such that when infants are positioned prone, or with their left side down there is less likelihood of reflux. There are several small studies looking at pH probe readings with position change which show fewer events with infants in alternate positions, most improved while prone, but also showing benefit of the left side down. Positioning with left side down would appear counterintuitive, as positioning right side down does promote gastric emptying, but increases the potential for reflux.

Although significant head elevation may aid in decreasing reflux, modest elevation of the head of the bed likely offers little benefit.

It is imperative that infants in whom alternative positioning is employed be returned to supine positioning prior to discharge. Even infants with severe reflux are safer in a "Back to Sleep" position. In anticipation of parental modeling, the infant should be returned to supine sleep position well in advance of hospital discharge.

### ***Thickening of Feeds:***

The liquid nature of infant feedings predisposes to reflux, and so thickening of feedings may offer a hypothetical benefit in management of reflux. Several small studies have been published evaluating the effectiveness of thickening feeds, with substrates ranging from rice cereal to anti-reflux formulas which thicken

upon exposure to gastric acidity. Despite the variation in studies, a small meta-analysis appears to show benefit.

Rice cereal can be used to thicken formula, but its ability to thicken breast milk is questionable. The amylase present to varying degrees in breast milk break down the starches in cereal leading to a more watery appearance fairly quickly.

One of the other commercial thickeners, SimplyThick®, has been associated with NEC in both preterm and term infants. In light of this and a recent FDA warning, we are not using SimplyThick® in any infants.

## Pharmacologic Therapy

### ***Acid Blockade:***

Suppression of gastric acid secretion follows adult experience treating “Gastroesophageal Reflux Disease” or GERD. Acidic refluxate in the distal esophagus of adult patients causes discomfort, and chronic exposure predisposes the esophageal mucosa to malignant change. Physiologic differences in the neonate, including the pH of refluxate would challenge the validity of such treatment in the NICU.

Acidification of the gut favors growth of beneficial bacteria including bifidobacterium and lactobacillus, and discourages the growth of pathogenic enterics. The “prebiotic” activity of breast milk, mimicked by formula companies consists of non-digestible oligosachharides which pass to the distal gut, promoting a relatively acidic environment. For all of these reasons, acid blockade raises concern in the neonatal population.

### ***H2 blockers (ranitidine, famotidine, cimetidine):***

H2 receptor antagonists are a class of agents which block histamine receptors in the gastric mucosa, decreasing acid secretion both basally, and in response to stimulation. Each of the drugs has been studied, although not as well as one might expect, with concerns raised regarding the safety of each. Famotidine was shown to decrease emesis in one study, yet was linked with the development of abnormal behaviors. A study involving cimetidine for prevention of chronic lung disease was stopped by the safety monitoring committee for an increase in death or IVH in the study group. A study by Wheatley and colleagues evaluating the efficacy of reglan and ranitidine found placebo to be more effective than the treatment group. Most concerning is a large study undertaken by the NICHD which in logistic regression analysis showed ranitidine to be an independent risk factor for the development of NEC. ***Given the absence of proven benefit, and the potential for harm, the use of H2 blockers for the treatment of reflux cannot be supported.***

### ***Proton pump inhibitors (lansoprazole):***

Similar justification for use to H2 blockers. Far more powerful in their ability to neutralize gastric pH by direct action on proton pumps. Their use has grown dramatically over the past few years, yet are being used off label in children < 12 months of age. Concerns from use in older patients include the risk of sepsis, C. diff infection, and increased fractures, thought related to calcium absorption. The implications of use in neonates, and osteopenia have not been studied.

A randomized trial evaluating the efficacy in treatment of infants failing drug therapy for reflux showed no benefit to lansoprazole therapy. A recent meta-analysis considering 12 studies of proton pump inhibitors found no benefit in treatment of infants with GERD. ***Given the absence of proven benefit, and the potential for harm, the use of proton pump inhibitors for the treatment of reflux cannot be supported.***

### ***Prokinetic agents:***

Pro-kinetic agents in the treatment of reflux are employed based on the assumption that promoting distal motility, and gastric emptying may decrease reflux episodes. It increasingly appears that in the premature and neonatal population, the tone of the lower esophageal sphincter plays a larger role than gastric emptying.

### ***Erythromycin:***

Erythromycin is a motilin analog, and has been studied in children to decrease feeding intolerance. Used in sub-antimicrobial doses, erythromycin does appear to decrease the length of time to feedings. There is not a clear dose range established, and there are concerns regarding the safety of erythromycin's use. Exposing infants to any antibiotic chronically may predispose them to developing resistant bacteria. The use of erythromycin in premature infants has also been linked to the development of pyloric stenosis. There is no useful data regarding the use of erythromycin in reflux.

### ***Metoclopramide:***

Reglan is a dopamine receptor analog which is able to cross the blood brain barrier. Multiple studies documenting complications including central symptoms such as drowsiness, irritability, tardive dyskinesia led to an FDA black box warning regarding its use. Surprisingly little data to support the use of metoclopramide in neonates for treatment of reflux. The most comprehensive review of 11 studies of metoclopramide use in neonates found insufficient evidence to support metoclopramide therapy. Of 5 randomized controlled trials, 2 found no benefit, and 2 showed significant placebo effect. Of 11 studies considered, 4 showed significant adverse events in the treatment group including dystonic reactions. ***Given the absence of benefit, and the potential for harm, the use of metoclopramide for the treatment of reflux can not be supported.***

## **Recommendations**

- There is no definition of GERD in the neonate, therefore treatment of "reflux" in an otherwise normal infant should only be considered if spitting interferes with weight gain.
- The diagnosis of reflux can be made clinically. Further invasive studies offer little to guide treatment.
- If treatment is to be undertaken, consider positioning first.
- If no response to positioning, consider thickening of feeds with rice cereal. The use of commercial thickeners containing xanthum gum (such as SimplyThick®) should be avoided.
- Pharmacotherapy for reflux has not been shown to benefit infants with reflux. Ranitidine, proton pump inhibitors, and metoclopramide have all been shown to potentially cause harm. As such, these agents should not be used in the treatment of reflux in otherwise normal infants.
- As reflux symptoms improve with maturation, any treatment initiated should have a trial of discontinuation prior to discharge.

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