PEDIATRIC NEWBORN MEDICINE CLINICAL PRACTICE GUIDELINES

Use of Acid-Suppressing Medications in the NICU – May 2019

BWH

PARTNERS HEALTHCARE

Clinical Guideline Name	Use of Acid-Suppressing Medications in the NICU
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Approved By	Dept of Pediatric Newborn Medicine Clinical Practice Council

Clinical Practice Guideline: Use of Acid-Suppressing Medications in the NICU

Points of emphasis/Primary changes in practice:

1. No NICU policy on use of acid-suppressing medications exists.

2. Recent publications suggest increasing evidence of harm from using these medications in the preterm or neonatal population, lack of benefit for many conditions commonly cited as indications for use, and widespread variability in the prescription of these medications by clinicians in the NICU.

3. The overall goal is for the multidisciplinary NICU clinical team to decrease variability in clinical practice surrounding use of these medications, and to appropriately identify infants who might benefit from this treatment as well as those for whom the treatment is not indicated. In addition, the team should identify goals of treatment when initiating acid-suppressing medications and be prepared to discontinue the treatment if ineffective.

Rationale for change: Creation of new policy.

Questions? Please contact: Dr. Katherine Bell

I. Purpose

The purpose of this clinical practice guideline is to (1) summarize current evidence regarding possible indications for usage of acid-suppressing medications in the preterm and neonatal population, (2) increase awareness of potential harm from use of these medications, and (3) reduce variability in clinical practice in the way in which acid-suppressing medications are prescribed in our neonatal intensive care unit (NICU).

II. Scope

This guideline applies to infants in the NICU, with emphasis on infants born preterm. The scope of this guideline includes the identification of appropriate candidates for prescription of acid-suppressing medications, description of the pharmacology of various agents including histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), and identification of goals of treatment and criteria for discontinuing therapy after initiation.

III. Background and Evidence Summary

PPIs and H2RAs have become some of the most frequently prescribed medications in the pediatric population. Even though their effectiveness for treatment of certain peptic conditions in children older than 1 year has been shown, there are very few studies in neonates and infants, resulting in extreme variability in utilization patterns among centers. There is a need for identification of high-risk populations and establishment of evidence-based protocols regarding administration of acid-suppressive agents.

Pathophysiology

Gastroesophageal reflux (GER) is classified as the retrograde flow of gastric content (refluxate) into the esophagus, with or without regurgitation or vomiting, and is physiologically normal, resulting from a temporary relaxation of the lower esophageal sphincter (LES). GER generally lasts less than three minutes and causes little to no symptoms. GER is very common in most infants. Though GER may cause discomfort in children and adults, usually through acidity and/or quantity of gastric contents, there is little evidence that GER causes harm in infants.[1] If GER results in harmful symptoms or complications it is then classified as gastroesophageal reflux disease (GERD).

Clinical symptoms that clinicians sometimes attribute to GERD include feeding intolerance, poor growth, apnea, desaturation and bradycardia, and worsening pulmonary disease. Behavioral signs commonly attributed to GERD include arching, irritability, and apparent discomfort associated with feeds. However, none of these signs or symptoms have been shown to be associated with objectively measured GER episodes in clinical studies.[1] Furthermore, several studies have shown that most reflux episodes in infants are non-acidic.[3] This is likely attributable to immature acid-producing parietal cells and the frequent and continuous feedings in the NICU which constantly buffer the acidity of stomach contents, making esophageal reflux less likely to be acidic.

Pharmacology

Acid-suppressing medications work to decrease the amount of hydrochloric acid (gastric acid) secreted in the stomach, thereby decreasing potential discomfort to the infant exhibiting acidic gastroesophageal reflux. Gastric acid production is regulated by the enzyme hydrogen potassium adenosine triphosphatase (H^+K^+-ATPase), also known as the proton pump. The proton pump is located on the basolateral membrane of parietal cells in the wall of the stomach and is stimulated to secrete gastric acid by activation of three parietal cell receptors: muscarinic-3 (M_3), cholecystokinin-2 (CCK_2), and histamine-2 (H_2) receptors.

H2RAs compete with histamine for binding to the H_2 receptor on parietal cells, which decreases stimulation of the proton pump and secretion of gastric acid by about 70%.[1,26] The proton pump can still be stimulated to secrete gastric acid by activation of the M_3 and CCK_2 parietal cell receptors. Enteral absorption is rapid and onset of activity occurs within the first hour. Peak levels are reached within 1-3 hours of enteral administration and within 30 minutes of intravenous administration. There has been diminished effect reported with chronic H2RA use, which may not respond to dose increases.[26]

PPIs irreversibly inhibit H^+K^+ATPase (the proton pump), a gastric parietal cell enzyme that is involved in the last step of acid secretion, resulting in an 80-95% decrease in gastric acid secretion.[1,26] The onset of action is within the first hour and peak levels are reached within 1-3 hours, however, maximal inhibition of acid secretion may take 2-5 days.[26] One dose inhibits around 50-70% of parietal cells, since not all proton pumps or parietal cells are active at any given time and therefore are not able to be antagonized. PPIs achieve similar acid blockade as H2RAs on day 1 of therapy.

Currently, two H2RAs and two PPIs are approved by the United States Food and Drug Administration (FDA) for use in infants <1 year, but only one for use in neonates <1 month. Famotidine is approved for use in infants < 1 year old for short-term treatment (≤ 4 weeks) of symptomatic GERD and ranitidine is approved for use in erosive esophagitis and in GERD for infants ≥ 1 month of age. Omeprazole and esomeprazole are approved for use in GERD-associated erosive esophagitis in patients ≥1 month of age.

Evidence Summary for Use of Acid Suppression in the Neonatal Population:

Acid-suppressive medications are among the most frequently prescribed medications in the NICU and their use has increased multifold over recent years.[2] It is estimated that almost one quarter of NICU patients receive these medications while hospitalized and the majority are continued after discharge.[4, 5] Despite increased use, acid-suppressive medications have not been shown to be effective in treating any of the reported symptoms of GERD. In a few randomized, double blind placebo-controlled trials, infants who received PPI had no significant decrease in a variety of symptoms attributed to GERD (i.e. crying, irritability) compared to those who received placebo, despite resultant esophageal and gastric pH increase.[2,6,7] One study showed no

significant difference in growth velocities in preterm infants with GER.[8] Although early studies suggested an association between apnea of prematurity and reflux, most studies do not support reflux as a cause of pathologic apnea in premature infants.[9-11] One trial of ranitidine actually showed worsening of bradycardia during treatment when used in conjunction with metoclopramide.[12] In regards to worsening pulmonary disease, there is no evidence that acid-suppressive medications affect the clinical course of bronchopulmonary dysplasia (BPD) despite reflux episodes being more common in infants with BPD.[13,14] In summary, there is no evidence of benefit for use of acid-suppressing medications among preterm infants with clinical symptoms of GERD, and apnea or bradycardia of prematurity. The AAP recently (July 2018) released a policy statement on management of GER in preterm infants and "strongly suggest that these agents should be used sparingly, if at all, in preterm infants."[1]

There are certain conditions for which acid-suppressive medications may have benefit in infants older than 1 year and children (erosive esophagitis, stress ulcer prophylaxis) although these all remain controversial. There is no high-quality evidence supporting use of acid-suppressing medications in infants under 1 year or preterm infants.

Determining Treatment Success
Monitoring for therapeutic success of acid-suppressing medications is especially challenging as symptoms commonly attributed to GERD are not predictive of response to therapy.

Safety & Adverse Effects:
There is growing evidence that acid suppression is associated with adverse effects on infants. These include:

- **Pneumonia and respiratory infections:** Multiple studies, including randomized trials[2], have shown that PPI use was associated with increased risk of community acquired pneumonia and other lower respiratory tract and lung infection in pediatric and adult populations. Several studies in the ICU setting have shown increased risk of ventilator associated and nosocomial pneumonia with acid-suppressive medication use. [21, 32]
- **Necrotizing enterocolitis (NEC):** Multiple studies have shown a link between H2RA use and NEC. Two large, multicenter retrospective studies of very low birthweight (VLBW) infants reported significantly increased risk of NEC among infants prescribed H2RAs in the NICU, even after controlling for clinical risk factors; one (n=11,072) showed a 1.7 times greater risk of NEC[22] and the other (n> 100,000) found 1.14 times greater odds of the combined outcome of death, NEC or sepsis. In the larger study, longer duration of exposure was associated with greater risk, and infants were more likely to suffer adverse outcome on a day they received the H2RA.[30] Finally, a study of 274 VLBW or very preterm (gestational age 24-32 weeks) infants showed a 6.6 fold increased rate of NEC in

infants exposed to ranitidine regardless of dosage or duration of therapy, despite no significant difference in gestational age, birthweight, gender, Apgar scores, duration of intubation, or intraventricular hemorrhage rates between groups.[29]

- **Other gastrointestinal infections:** Both H2RAs and PPIs have been shown to increase risk of gastrointestinal infections in infant, pediatric and adult populations. Known side effects of H2RA's and PPI's include reduced gastric acidity, delayed gastric emptying, increased mucous viscosity, modification in microbiota, and impairment of neutrophil function. These all potentially contribute to increased risk for infection.[4]
- **Systemic infections:** One prospective cohort study in VLBW infants born between 24-32 weeks gestational age found that acid-suppressive medications were associated with higher incidence of sepsis, pneumonia and urinary tract infection.[23, 29] One large observational study showed an association with ranitidine use in the NICU and 7-times increased risk for late onset sepsis compared to NICU infants not exposed to ranitidine.[24]
- **Increased risk for bone fractures:** Changes in gastric pH decrease calcium absorption leading to adverse effects on bone mineralization and may increase risk for fractures.[4]
- **Increased risk for allergic disease in childhood:** One large retrospective cohort study found that either H2RA use or PPI use in the first 6 months of life was associated with atopic disease (i.e. asthma, allergic rhinitis and conjunctivitis, eczema), food allergy, medication allergy, and urticaria later in childhood.[25]

Other reported side effects:

- Spontaneous bacterial peritonitis, abdominal pain, Celiac Disease, constipation, diarrhea, gastric polyps, malabsorption of micronutrients (including magnesium, iron, vitamin C and vitamin B_{12}), microbiome changes, nausea, rebound acid hypersecretion, acute interstitial nephritis, anemia, cough, death, fever, flushing, headache, increased liver enzymes, irritability, somnolence, head banging, brady-arrhythmia.

Safety concerns in specific patient populations:

VLBW infants: Special care should be taken when considering the use of acid-suppressing medications in VLBW infants. Use of H2RAs in VLBW infants has been associated with NEC, infection, and death in a small, retrospective, cohort study;[29] with NEC in a large, retrospective, case-control study;[22] and with the combined outcome of death, NEC, or sepsis in a very large retrospective cohort study.[30]

SUMMARY OF RECOMMENDATIONS:

Given the lack of evidence for benefit of acid-suppressive pharmacotherapy in the neonatal period, growing evidence of adverse effects, and national guidelines recommending against their use—particularly in preterm infants—**we recommend limiting use of acid suppressive medications in the NICU** to a small selected group of infants for which other interventions are ineffective. **We also specifically recommend against starting acid-suppressive medications for apnea of prematurity and routine reflux.** These recommendations are summarized in the following table:

INDICATIONS FOR WHICH ACID SUPPRESSION CAN BE CONSIDERED	**INDICATIONS FOR WHICH ACID SUPPRESSION IS NOT RECOMMENDED**
Compromise of esophageal or gastric lining (ie. Bloody emesis or NG output)*	• Frequent regurgitation or vomiting • Irritability • Apnea, bradycardia or desaturation • Chronic lung disease • Stress gastrointestinal prophylaxis

* Treatment should be initiated symptomatically and be continued until symptoms resolve.

In addition, we recommend particular care when considering acid suppressive medication for an infant who is <37 weeks postmenstrual age or birthweight <1500 grams due to potentially increased risk of adverse effects in these populations.

Pharmacotherapy Trial:

If clinician desires starting acid-suppressing medication for a non-indicated use as a last resort, start one acid-suppressing medication (either PPI or H2RA) as a **TRIAL.**

A PHARMACOTHERAPY TRIAL CONSISTS OF:	
Define Treatment Goals	• Clearly state specific problem that may benefit from medication and desired result (i.e. decreased episodes of feeding refusal, increased PO intake, etc.)
Determine Duration of Pharmacotherapy Trial	• Trial should last no more than 7 days (based on pharmacology of acid suppressing medications)

Document DAILY	• Use EPIC smartphrase ".nicuacidsuppressingmed"
	  • Number of days on trial
	  • If defined goals are met

Discontinuation	• Discontinue if no significant improvement after trial

Formulary and Dosing:

PPIs are recommended over H2RAs for reflux-related erosive esophagitis in infants with GERD.[27] Considerations when choosing between PPIs and H2RAs include efficacy, safety, clearance, administration route, onset/time to maximum effect*, and cost.

Class	Acid Suppression	Drug on Formulary	Route	Metabolism/ Elimination	Cost
Proton Pump Inhibitor	80-95%	Omeprazole	PO	Hepatic	$
		Pantoprazole	IV		$$
Histamine-2 Receptor Antagonist	70%	Famotidine	PO	Renal	$
			IV		$

***** PPIs achieve similar acid blockade as H2RAs on day 1 of therapy (see Pharmacology section for details).

For dosing recommendations, see NICU Drug Administration Guidelines.

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