Reducing Antacid Use in a Level IV NICU: A QI Project to Reduce Morbidity

Richelle M. Reinhart, MD†; Jacquelyn D. McClary, PharmD**; Mengqi Zhang, PharmD**; Jaime L. Marasch, PharmD**; Anna Maria Hibbs, MD*; Mary L. Nock, MD*

INTRODUCTION
Gastroesophageal reflux (GER) is a physiologic occurrence in infants. Clinicians caring for neonates use histamine-2 receptor antagonists (H2As) or proton pump inhibitors (PPIs) for symptomatic reflux, apnea/bradycardia/desaturations, or irritability. Recent studies have shown that there is an increased incidence of infection, fracture, and mortality in neonates who receive antacids.

Methods: A multidisciplinary team aimed to decrease nonindicated antacid use in the NICU by 50% by April 2019. Outcome measures include the median number of inappropriate antacid prescriptions and patient-days on acid-suppressants. Interventions include education regarding use and risks of antacids, development of a list of indications deemed "appropriate" for starting an H2A or PPI, mandatory discussion on rounds when considering antacids, documentation of treatment goal, and indication, and an automatic drop-off in the electronic medical record. Results: Baseline data (June–December 2017) showed 19 prescriptions of H2As or PPIs. Of those, 10 orders were deemed “inappropriate,” according to our indicated uses. There were 407 total patient-days of medication-use (median: 51 patient-days). After the implementation of the interventions (October 2018–May 2019), there were 11 prescriptions of antacid medications, 3 of which were deemed “inappropriate.” There were 206 total days of medication-use (median: 18.5 patient-days). Conclusions: A multidisciplinary agreement on indications for antacid use in neonates stimulates discussion and creates more purposeful use. Overall, we successfully decreased nonindicated antacid prescriptions in the NICU. For the next steps, we hope to educate physicians on the risks of antacid use and reduce prescriptions in other areas of the hospital and the outpatient setting.

From the *Division of Neonatology at University Hospitals Rainbow Babies and Children’s, Cleveland, Ohio, USA

Preliminary data were presented at the Neonatal-Perinatal Conference at Nationwide Children’s Hospital in Columbus, Ohio. The principal investigator presented this research at Rainbow Babies and Children’s Residents’ Research Day in Cleveland, Ohio.

*Corresponding author. Address: Richelle M. Reinhart, MD, 11100 Euclid Ave, Cleveland, OH 44106 PH: 216-844-0205; fax: 216-844-7166
Email: Richelle.Reinhart@UHHospitals.org

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

To cite: Reinhart RM, McClary JD, Zhang M, Marasch JL, Hibbs AM, Nock ML. Reducing Antacid Use in a Level IV NICU: A QI Project to Reduce Morbidity Pediatr Qual Saf 2020;3:e303. Received for publication November 4, 2019; Accepted April 22, 2020. Published online May 12, 2020. DOI: 10.1097/pq9.0000000000000303

Symptoms thought to be due to reflux, including apnea, bradycardia, desaturations, failure to thrive, discomfort, or feeding intolerance. Recent literature is confirming that these “symptoms” are not correlated with GER and, therefore, do not warrant treatment.

Histamine-2 receptor antagonists (H2As) or proton pump inhibitors (PPIs) are used for symptoms of reflux in neonates. As with many medications in neonatology, there has not been FDA approval of antacids in neonates. PPIs and H2As are not effective in treating reported reflux-related symptoms. Furthermore, these medications have safety concerns. Gastric acid is a barrier against pathogens, and there is significant literature showing that patients using acid suppressants are at an increased risk of infections. In hospitalized adults, there are a higher number of nosocomial pneumonia diagnoses in those taking acid-suppressing medications. There is a higher risk of acute gastroenteritis and community-acquired pneumonia in children taking antacids. Additionally, gastric acid plays a role in oral food antigenicity, and in vitro studies indicate that antacid medications are a risk factor for food sensitivities.

In neonates, there is evidence that infants using acid suppressants are at a higher risk for bloodstream infections, increased mortality, pneumonia, and respiratory events. There is an association between very low birth
weight infants on H2As and necrotizing enterocolitis. This finding supports data showing that the gastric pH level may play a role in the pathogenesis of necrotizing enterocolitis; introducing medications that increase this level may put infants at risk. Additionally, contrary to the common thought that reflux increases apneas, bradycardic events, and desaturations, it is more likely that these cardiorespiratory events temporarily relax the lower esophageal sphincter which then causes reflux of stomach contents. Last, recent evidence has shown that infants who received PPIs had an earlier median first fracture age. This risk is higher with a longer duration of antacid administration or earlier use of the antacid.

Although these risks are significant, there is some evidence in support of these medications. After surgical correction of esophageal atresia (EA), the use of antacids may help to reduce postanastomotic esophageal strictures, which are the most common complication of surgical repair and are associated with postoperative GER. Patients with EA are at an increased risk for acid reflux due to abnormal development of the esophageal smooth muscle, impaired peristalsis, and inadequate lower esophageal sphincter function. Recent consensus guidelines recommend using PPIs for the first year of life. Patients with Pierre Robin Sequence often experience airway obstruction secondary to their anatomic abnormalities; many practitioners prophylactically initiate antacids to prevent GER leading to laryngeal and pharyngeal edema. In patients with short bowel syndrome who experience gastric hypersecretion, antacid medications are recommended in the acute phase after resection.

Recently, the American Academy of Pediatrics Section on Neonatal-Perinatal Medicine made reducing the use of antireflux medications for the treatment of reflux a Choosing Wisely initiative. For this reason, and in light of the evidence of risks mentioned earlier, we established a goal to decrease the use of antacids in the Rainbow Babies and Children’s NICU.

METHODS

Setting

The Rainbow Babies and Children’s Hospital NICU is a Level IV NICU with a transitional nursery, a total of 82 beds. Rainbow is part of the University Hospitals Cleveland Medical Center, an academic medical center located in Cleveland, Ohio. There are 16 medical divisions as well as 12 surgical specialties at this tertiary referral center. Rainbow is contiguous with the MacDonald Women’s Hospital, so medical professionals care for both inborn and outborn patients in the NICU and NICU Transitional Nursery. Neonatology fellows, pediatric residents, neonatal nurse practitioners, and neonatal pharmacists work together to care for these infants. In 2018, 1,048 infants were admitted to Rainbow’s NICU; in 2019, there were 1,338 infants admitted. Of those patients, 142 in 2018 and 162 in 2019 were under 1500 g. Between 2017 and 2019, there were a total of 71 infants treated for surgical conditions (ie, congenital diaphragmatic hernia, Hirschsprung’s, neural tube defect, gastrochisis, omphalocele, duodenal/jejunal/ileal atresia, tracheoesophageal fistula/EA, or imperforate anus).

IRB Approval

This project is a quality improvement project and was determined by the University Hospitals Cleveland Medical Center IRB to be nonhuman subjects research.

Baseline Data

For baseline data collection, we performed a retrospective chart review to include all infants in the NICU and NICU Transitional Nursery who were prescribed PPIs or H2As from June to December 2017. The team reviewed their charts for indications of antacid medication initiation. During this time, the team conducted a literature review to find evidence supporting when to use acid suppression in specific diagnoses. Our team created a key driver diagram to develop a variety of interventions to attain the goal of reducing morbidity by decreasing antacid medication prescriptions. The SMART aim is to reduce the use of antacid medications in patients without indications in the NICU/Transitional Nursery by 50% by April 30, 2019 (Fig. 1). Data were not collected between baseline and intervention dates (January to October 2018) as the team used this time for literature review and preparation for intervention implementation.

Implementation of Interventions

A multidisciplinary team was created, including otolaryngologists, general pediatric surgeons, pharmacists, and neonatologists. This team used neonatal and pediatric background literature to develop a list of indications considered “appropriate” to start an acid suppressant. We did not create this list to be a description of when acid suppressants are required, but instead as a list of indications of when practitioners could consider these medications. The list of indications was presented to the NICU faculty at Rainbow Babies and Children’s for review and consensus. The final approved indications list is as follows: tracheoesophageal fistula/EA, within 1 month of upper airway surgery, short gut/ostomy with increased output, gastric anastomosis, bloody gastric aspirates/emesis, vocal cord granulomas with a 1-month trial followed by rescoping, and suspected clinically significant acid reflux in babies unable to tolerate a pH probe study (trial of antacids for 2 weeks).

All members of the multidisciplinary team, including subspecialty surgeons and neonatology, approved this list of indications. However, only representatives from pharmacy and neonatology are typically present for the discussion of medication initiation during morning rounds. One exception is if initiation is for one of the “preapproved” surgical indications, in which case both neonatology and surgery are present in the postoperative period to agree on the antacid.
For implementation, the team provided education regarding risks and benefits of antacids to the NICU caregivers (including pharmacists, neonatologists, nutritionists, pediatric residents, neonatal nurse practitioners, nursing staff, and neonatology fellows) during monthly quality improvement meetings. In total, the team attended 3 sessions. The team disseminated information regarding the risks of antacids and appropriate indications for the initiation of these medications to the neonatal nurse practitioners and pediatric residents, who act as primary ordering providers. The neonatal pharmacists provided similar education on rounds before the introduction of any antacid medication. Additionally, the NICU nursing staff held a journal club focused on antacid use in neonates to help promote discussion of its risks and benefits, the indications for use, and the signs and symptoms of reflux.

Our team distributed the guideline with indicated uses on October 1, 2018, for use in all patients in the NICU and Transitional Nursery. Pharmacy representatives present during rounds initiated conversation using the guideline and documented those who were present and for which indication the practitioners started the medication. This mandatory discussion acted as another intervention to stimulate debate and reduce unnecessary use. The documentation served as a tracking tool for our project to record all antacid prescriptions (Fig. 2).

Last, the team implemented an automatic end date of 2 weeks through the electronic medical record (EMR) to promote discussion regarding the infant’s status after a trial of the PPI or H2A. This automatic end date provided another opportunity to re-evaluate the infant’s need for acid suppressants and offered an additional chance for education regarding the risks of these medications.

**Data Collection**

The primary outcome measure is the median number of acid-suppressing prescriptions determined to be inappropriate; the secondary measure is the number of patient-days on these medications, which reflects the overall exposure of antacid for all infants in the NICU over a specific period. This measure was calculated by adding together the total number of days all infants received an antacid during each month. The balancing measure of this project is the number of patients with suspected or possible gastric bleeding. This balancing measure was chosen because we are limiting antacid use to specific indications, eliminating those instances in the past where antacids may have been prescribed prophylactically to avoid gastritis or gastric bleeding, such as in addition to steroid use or postoperatively. The guidelines we implemented would not allow this use. As we were already tracking antacid implementation for visible gastric bleeding, we were able to see if there was more evidence of gastric bleeding post-guideline without the prophylactic use of antacid medications.

Data collection after implementation occurred prospectively by the collection of all guidelines documentation completed on NICU rounds. An additional retrospective chart review occurred by looking through all patients during the implementation period on the NICU and Transitional Nursery to ensure there were no prescriptions that occurred without documentation.

---

**Fig. 1.** Key driver diagram.
RESULTS
Baseline data showed 18 infants started on a PPI or H2A, with 19 prescriptions total (Fig. 3). One baby had 2 different prescriptions written during his hospitalization, each at a different time for various indications. Reviewing these 19 indications using the guideline, 10 prescriptions (53%) were “inappropriate”. During the 7 months of baseline data, the median number of nonindicated orders

---

Fig. 2. Tracking sheet for data collection as well as a list of indications for appropriate reasons to start antacid medications. TEF.
The average number of patient-days per month was 2 (Fig. 4). The total number of patient-days on these medications was 407 days, with a median of 51 patient-days per month (range: 24–78) (Fig. 5). The average number of days each infant was on an antacid before implementation was 23.1 days (median: 10, range: 1–114).

Postimplementation, there were 11 infants started on a PPI or H2A. Three of these did not follow the guideline and are considered “inappropriate” indications (Fig. 3). The median number of nonindicated prescriptions per month was one-half of an order, a decrease of 75% from baseline (Fig. 4). The total number of patient-days on these medications postimplementation was 206, a 49% reduction from the baseline data of 407 days (Fig. 5). As can be seen in the run chart in Figure 5, this reduction is considered a nonrandom shift in the data, as there are 6 consecutive points below the baseline median. The median patient-days per month that patients were on antacids after interventions decreased to 18.5 days (range: 9.5–63). The average number of days each infant was on an antacid medication postimplementation was 18.7 (median: 13 days, range: 1–58).

Adverse Events
Our balancing measure for this project is the number of patients with evidence of gastric bleeding. After the implementation of the interventions, we noted an increased number of patients with possible gastric bleeding (documented as blood-tinged gastric output) as an indication to begin antacid therapy. Upon retrospective review and consideration of the reasons for antacid use in the baseline period (Fig. 3), it appeared that none of these patients had a reason for which they would have been started on antacids before the implementation of the indications list (use with systemic steroid administration, postoperatively, etc.). Therefore, we thought it unlikely that the implementation of antireflux medication restrictions led to an increase in gastric bleeding.

DISCUSSION
Implementation of the interventions described earlier was effective in Rainbow’s NICU. We did meet the primary goal of decreasing the median number of inappropriate prescriptions by 50%, as noted by the reduction from 2 nonindicated orders per month to one-half. It should be noted that this is not a dramatic change in prescriptions, which is reflective of our low baseline number of antacid prescriptions. Perhaps even more importantly, the team also reduced the secondary outcome measure (patient-days on antacids) by more than 50%. The average number of days that an infant was on an antacid in the postimplementation period decreased; however, the median increased. We believe that this occurred because, before implementation, many babies stayed on antacids for a significantly longer time, as evidenced by the range, up to 114 days, which reflects a decrease in the mean. This change is primarily due to the EMR drop-off period limiting antacid trials to 14 days.
Previously, there was not a guideline for initiating antacid medications; having a multidisciplinary team create the guideline likely had the largest effect on decreasing antacid usage. We noted that before this project, individual clinicians initiated antacids based on their previous experience, limited knowledge of the risks antacids, and recommendation from consulting subspecialists who may also have limited understanding of the risks in a neonatal population. Exploration of the risks of antacids stimulated much discussion during QI meetings and NICU rounds. During a discussion of how Rainbow’s neonatologists use antacids, clinicians anecdotally felt that the number of prescriptions was low and that the number of orders for indications not agreed upon in the guideline would be
low. This impression is correct in comparison to a similar project done at Boston Children’s, where practitioners prescribed antacids 11.5 times per month. Although our clinicians felt that antacid use was already compliant with the indications selected, this was not always the case per the baseline data, and there was a lack of recognition of the prolonged courses of treatment that patients were receiving.

In addition to decreasing inappropriate antacid prescriptions, we also reduced the NICU patients’ overall antacid exposure. Creating the EMR automatic drop-off time was likely the driver behind reducing the number of antacid patient-days. There previously was no consensus on how long a patient should be trialed on an antacid when reflux or symptoms of reflux were suspected. This lack of consensus led to clinicians starting acid suppressants and then continuing the medications without reassessment of symptoms or whether they could trial off the medication. Now, there is a designated time to discuss symptom improvement and whether the practitioner can discontinue the antacid.

This project was feasible in a large NICU and is generalizable to similar patient populations. Other institutions may find that there is not a consensus as to which patients should trial antacid medications. Additionally, clinicians in areas outside of the NICU, such as on a general pediatrics floor where infants receive care, could introduce similar guidelines. To create sustainability, the team has continued to educate surgical subspecialties regarding antacid indications. This education is important when new physicians with different opinions and experience join the practices. The conversation continues to be ongoing, even at this time in our NICU; the subspecialty services also continue to provide evidence when antacids are indeed indicated and educate the neonatologists regarding these circumstances. Since the initiation of this project, there have been further meetings between subspecialties to reach consensus again on the importance of reducing neonates’ exposures to these medications. It may be helpful for other NICUs looking to implement a similar guideline to create an “Antacid Stewardship” program. For instance, the list of indications in an EMR could be tailored to specific, approved indications with automatic drop-offs specific to that indication. Additionally, there is a significant amount of sustainability that lies with the pharmacy representatives in our NICU, as those team members can continue spreading education and have sustained oversight of medication initiation.

Future Considerations
It is important to note that there were relatively few prescriptions written for H2A and PPIs even before intervention implementation. Although the interventions did decrease nonindicated antacids in the NICU, there is still work to do in the outpatient setting. A recent article studying the association between antacid prescriptions and antibiotics with increasing allergic disease in early childhood showed that approximately 9.3% of infants under the age of 6 months were started on an antacid. Neonates in other areas of the hospital, such as the Cardiothoracic Intensive Care Unit, are also at risk for infection and NEC, and we must address any unnecessary use of antacid medications in those areas as well.

CONCLUSION
There is significant evidence that acid-suppressing medications should be used carefully in pediatric patients, particularly in the NICU, where neonates are susceptible to infection. The AAP’s Choosing Wisely Neonatology campaign highlights these risks and the importance of proper use of antacids. Implementation of a literature-based usage guideline, education, thoughtful discussion before initiation, and EMR interventions can reduce the use of unnecessary antacids. Clinicians could implement similar interventions at other large hospitals with neonatal units looking to decrease inappropriate antacid use.

DISCLOSURE
The authors have no financial interest to declare in relation to the content of this article.

ACKNOWLEDGMENTS
Thank you to the NICU faculty at the Rainbow Babies and Children’s Hospital for their support and collaboration during this project; the NICU pharmacy team for assistance with data collection and education; Dr. Carissa Wentland for her contributions regarding the Ear, Nose, and Throat literature and the use of antacids; Dr. Eiichi Miyasaka for his contributions regarding the Pediatric Surgery literature and the use of antacids.

REFERENCES
1. Eichenwald EC. Diagnosis and management of gastroesophageal reflux in preterm infants. *Pediatrics.* 2018;142:e20181061.
2. Peter CS, Spadowski N, Bohnhorst B, et al. Gastroesophageal reflux and apnea of prematurity: no temporal relationship. *Pediatrics*. 2002;109:8–11.

3. Orenstein SR, Hassall E, Furmaga-Jablonska W, et al. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr*. 2009;154:514–520.e4.

4. Dermyshi E, Mackie C, Kigozi P, et al. Antacid therapy for gastroesophageal reflux in preterm infants: a systematic review. *BMJ Paediatr Open*. 2018;2:e000287.

5. van der Pol RJ, Smits MJ, van Wijk MP, et al. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. *Pediatrics*. 2011;127:925–935.

6. Nylund CM, Eide M, Gorman GH. Association of *Clostridium difficile* infections with acid suppression medications in children. *J Pediatr*. 2014;165:979–984.e1.

7. Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. *Aliment Pharmacol Ther*. 2011;34:1269–1281.

8. Herzig SJ, Howell MD, Ngo LH, et al. Acid-suppressive mediation use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301:2120–2128.

9. Canani RB, Cirillo P, Roggero P, et al; Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics*. 2006;117:e817–e820.

10. Pali-Scholl I, Jensen-Jarolin E. Anti-acid medication as a risk factor for food allergy. *Allergy*. 2011;66:469–477.

11. Slaughter J, Stenger M, Reagan P, Jadcherla S. Neonatal H2-receptor antagonist and proton pump inhibitor treatment at US children’s hospitals. *J Pediatr*. 2016;174:63–70.

12. Guillet R, Stoll BJ, Cotten CM, et al; National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2006;117:e137–e142.

13. Abu Jawdeh EG, Martin RJ. Neonatal apnea and gastroesophageal reflux (GER): is there a problem? *Early Hum Dev*. 2013;89(suppl 1):S14–S16.

14. Di Fiore J, Arko M, Herynk B, et al. Characterization of cardiorespiratory events following gastroesophageal reflux in preterm infants. *J Perinatol*. 2010;30:683–687.

15. Malchodi L, Wagner K, Susi A, et al. Early acid suppression therapy exposure and fracture in young children. *Pediatrics*. 2019;144:e20182625.

16. Mousa H, Krishnan U, Hassan M, et al. How to care for patients with EA-TEF: the known and the unknown. *Curr Gastroenterol Rep*. 2017;19:65.

17. Amin SC, Pappas C, Iyengar H, et al. Short bowel syndrome in the NICU. *Clin Perinatol*. 2013;40:53–68.

18. Cladis F, Kumar A, Grunwaldt L, et al. Pierre Robin sequence: a perioperative review. *Anesth Analg*. 2014;119:400–412.

19. Angelidou A, Bell K, Gupta M, et al. Implementation of a guideline to decrease use of acid-suppressing medications in the NICU. *Pediatrics*. 2017;140:e20171715.

20. Mitre E, Susi A, Kropp LE, et al. Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. *JAMA Pediatr*. 2018;172:e180315.