Implementation of a Guideline to Decrease Use of Acid-Suppressing Medications in the NICU

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BACKGROUND AND OBJECTIVES: Acid-suppressing medications are used extensively in term and preterm newborns despite limited efficacy data and increasing evidence for potential harm. We sought to reduce nonindicated use of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) in our level III/IV NICU by developing and implementing a guideline for their use. Our specific aim was to reduce prescriptions among infants <1 month corrected age from a baseline of 7.5 to 4 per month by December 2016.

METHODS: Our outcome measures were number of nonindicated PPI/H2RA prescriptions per month, total (indicated and nonindicated) prescriptions per month and percent of patient days with PPI/H2RA therapy. We also tracked potential complications associated with PPIs/H2RAs as secondary outcomes and gastrointestinal bleed as a balancing measure. Interventions and plan-do-study-act cycles included implementation of the initial guideline, guideline revision based on staff feedback, and staff education. By using statistical process control charts and interrupted time series analysis, we compared outcomes over an 8-month baseline period and 2 postimplementation periods spanning 19 months.

RESULTS: Nonindicated prescription of PPIs/H2RAs decreased from mean 7.5 per month to 0 (P = .001). Concurrently, total PPI/H2RA prescriptions decreased from mean 11.5 per month to 2.5 (P = .002). Rates of the balancing measure and potentially related complications remained stable over time.

CONCLUSIONS: Implementation of an evidence-based guideline in our unit led to a significant decrease in nonindicated use of acid-suppressing medications and reduced the burden of exposure to PPIs/H2RAs. This intervention could feasibly be implemented in other similar inpatient settings.

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are some of the most frequently prescribed medications in the NICU. Despite limited safety and efficacy data in neonates, almost one quarter of NICU patients receive acid-suppressing medications, with the majority continued after discharge, although there is significant interhospital variation in prescription rates.1,2 Mounting evidence of adverse effects from acid-suppressing medications3–6 has raised concerns about their risk-benefit profile in infants. Recent guidelines recommend against routine usage of PPIs/H2RAs in both term and preterm infants,7 and the American Academy of Pediatrics “Choosing
Wisey” campaign recently identified usage in preterm infants as 1 of the top 5 unnecessary treatments in newborn medicine. 8 Acid-suppressing medications are most commonly prescribed in the NICU for gastroesophageal reflux (GER), apnea and bradycardia, bronchopulmonary dysplasia, airway anomalies, and bowel anomalies. 1-2 The lack of high quality evidence in infants prevents consensus regarding use for airway anomalies 9,10 and bowel anomalies such as esophageal atresia,7,11 which remain controversial. However, evidence clearly demonstrates no benefit from acid suppression for GER in term or preterm infants 12-15 or apnea in premature infants. 16-22

Although benefits of acid suppression in infancy seem increasingly unlikely, adverse effects from PPI/H2RA treatment are now well documented. Reduced gastric acidity, alteration of the gut microbiome and interference with neutrophil function result in increased risk of gastrointestinal infections in term infants 3 and necrotizing enterocolitis in preterm infants. 4,5,23 Treatment increases rates of community-acquired pneumonia even in healthy infants in the outpatient setting 23 and is associated with ventilator-associated pneumonia in the PICU 24 and late-onset sepsis in the NICU. 25 Gastric pH changes impede calcium absorption with potentially harmful effects on bone development and increased risk of fractures. 6 Adverse effects are of particular concern for neonates and premature infants, whose relative liver immaturity may result in delayed drug metabolism. 6

Because of these concerns, we assembled a quality improvement team to measure and reduce the nonindicated use of PPIs/H2RAs in our NICU. We sought to develop a guideline for prescription of acid-suppressing medications to foster change in prescribing behavior and reduce practice variation. 26

In addition to guideline development, we sought to use quality improvement methods to implement the guideline and ensure adherence. The specific aim of our project was to reduce the number of nonindicated PPI/H2RA prescriptions among infants <1 month corrected age from a baseline of 7.5 to 4 per month by December 2016.

METHODS
Setting
The Boston Children’s Hospital NICU is an academic tertiary and quaternary referral center serving infants ≤ 6 months old with complex medical or surgical conditions. More than 650 infants are admitted each year through the emergency department or transferred from other hospitals. More than 80% of these infants are <1 month corrected age at admission. All infants are cared for by a multidisciplinary team, including neonatologists, neonatal fellows, neonatal nurse practitioners, and NICU-dedicated nutritionists and pharmacists. The team caring for infants with surgical diagnoses additionally includes pediatric surgeons, pediatric surgical fellows, and surgical critical care fellows. Before this project, there were no guidelines regarding the use of acid-suppressing medications in our NICU, and prescription of these medications was per clinician discretion. Medication prescriptions are written by the neonatal fellow, surgical critical care fellow, or neonatal nurse practitioner in our unit.

Intervention
We assembled an interdisciplinary team of physicians specializing in neonatology (fellows and attending physicians, including the NICU medical director), pediatric surgery, and pediatric gastroenterology; NICU nurses; and neonatal pharmacists. Our team analyzed key drivers (Fig 1) and developed interventions to minimize nonindicated use of acid-suppressing medications. Interventions fell into 3 categories: (1) establishing evidence-based criteria for PPI/H2RA prescription and implementing them as a clinical practice guideline, (2) educating staff, and (3) encouraging staff buy-in and guideline uptake. Figure 2 shows a timeline of the interventions.

Guideline Development
Our team performed a literature review and agreed on the following evidence-based indications for prescribing a PPI/H2RA to infants <1 month corrected age: (1) lack of integrity of the gastric lining, 27 (2) esophageal atresia, 7 (3) otolaryngologic surgery or vocal cord edema and erythema with airway compromise, 9 (4) short bowel syndrome or presence of ostomy (due to association with gastric acid hypersecretion 28), and (5) systemic steroid therapy. 27,29 Prescription for these conditions was considered justifiable but not mandatory. Although many of these indications are controversial, there was not enough evidence to confidently exclude benefit from PPI/H2RA use in these conditions; therefore, use based on clinician judgment and local expert consensus was considered reasonable. Conditions specifically not supported by the guideline included nil per os (NPO) status, feeding intolerance, uncomplicated GER, and apnea and bradycardia. 12,13,16,17

In February 2016, we received feedback from clinical staff that a small subset of patients warranted a trial of acid-suppressing medication therapy for conditions not prespecified by the guideline; generally, these were difficult clinical cases (eg, patients considered for surgical intervention because of feeding problems) in which distinguishing between uncomplicated GER and symptomatic GER disease (GERD) was challenging.
We do not routinely use pH or impedance probes to diagnose GERD because of their invasive nature and lack of correlation with objective esophagitis, nor do we routinely use a reflux symptom index score. We revised the guidelines to include a medication trial for indications not specified by our original guideline; clinicians wishing to initiate a trial were then considered compliant if they documented the goal and length of the trial (up to 7 days based on H2RA/PPI pharmacokinetics), and objective criteria for deciding whether treatment was effective.

We excluded patients with congenital diaphragmatic hernia or receiving extracorporeal membrane oxygenation because they are cohort in a different unit in our hospital.

**Staff Education**

Before guideline implementation, our team spent 2 months familiarizing NICU staff with the guideline and addressing misconceptions about PPI/H2RA use. A team member provided in-person education at monthly staff meetings for physicians, nurse practitioners, and nurses. We posted a 1-page guideline summary in several locations in the NICU, particularly near the computers used to order medications and in the rounding workroom. After revision of the guideline in February 2016, we spent an additional 2 months reeducating staff, including rotating attending physicians, by using similar methods (Fig 2).

**Encouraging Staff Buy-In and Uptake**

We sent monthly reminder e-mails summarizing the guideline to the on-service physicians and nurse practitioners. A project team member visited the unit daily on weekdays during the first month after implementation to answer questions and subsequently team members were available by e-mail. By using the plan-do-study-act (PDSA) method, we assessed the success of our implementation process by reviewing outcome data every 2 months and made rapid cycle changes as needed to support uptake and adherence (Fig 2). Changes included: (1) recruiting our NICU nutritionists.
(who help clinicians write parenteral nutrition [PN] orders) to assess need for H2RA inclusion in PN on the basis of guideline criteria, (2) adding a notation to the nurses’ daily rounding sheet to ensure the indication for the medication was discussed on rounds, (3) providing an incentive of free lunch for the unit staff each week that they achieved 100% adherence to the guideline, and (4) assigning a dedicated staff member to collect data daily on rounds, enabling real-time data tracking and feedback.

**Data Collection and Measures**

We performed a retrospective chart review from February to September 2014 to obtain adequate data to assess the baseline rate and indications for acid-suppressing medication prescription. We then prospectively collected data for 19 months after guideline implementation, ending when the project had met its goal consistently for 6 months. We obtained census and demographic data from the Children’s Hospitals Neonatal Database. We identified all infants <1 month corrected age who were prescribed acid-suppressing medications (at least 1 dose enterally or intravenously, including in PN) from electronic prescription data, and tracked the number of PPI/H2RA prescriptions (both indicated and nonindicated) and the duration of therapy.

The primary outcome measure was the number of prescriptions each month that did not meet guideline criteria (ie, nonindicated prescriptions). Secondary outcomes included the total number of (indicated and nonindicated) PPI/H2RA prescriptions each month, and the ratio of patient days on which a PPI/H2RA was administered to total patient days each month for infants admitted at <1 month corrected age as a measure of overall burden of exposure.

In each period, we categorized the reasons for nonindicated prescriptions (by using chart review from the daily progress notes at the time of prescription) for analysis with Pareto charts. After guideline implementation, we requested that clinicians complete a paper form (Supplemental Fig 8) documenting the indication for new prescriptions. Starting in July 2016, a dedicated staff member completed the form during daily rounds.

The completion rate for paper-tracking forms served as our process measure.

Additional outcome measures were complications that have been associated with acid-suppressing medication use, including sepsis (defined as positive blood, urine, or cerebrospinal fluid culture results or clinical diagnosis resulting in treatment with antibiotics for at least 7 days), ventilator-associated pneumonia or tracheitis, necrotizing enterocolitis (Bell stage >1), and fracture (confirmed by radiograph). We also tracked gastrointestinal bleeding as an outcome that might indicate harm from withholding acid-suppressing medication. We retrieved this information from the Children’s Hospitals Neonatal Database and daily International Classification of Diseases, Ninth Revision billing codes.
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We analyzed the control charts with changes between each period and those process changes. Changes in median values of outcomes in each period were compared by Kruskal-Wallis test, and proportions were compared by χ² test.

Data were collected and managed by using Research Electronic Data Capture tools.²²

**Statistical Analysis**

We used statistical process control charts to analyze changes in the outcome measures over time.³¹ We used c-charts for the primary outcome measure of number of nonindicated and total prescriptions of PPIs/H2RAs because an infant could have >1 prescription during his or her hospitalization and the number of infants admitted each month was relatively constant. We used a p-chart for the secondary outcome measure of ratio of PPI/H2RA days to total patient days. Because there were significant differences in each outcome between periods, we identified process changes between each period and analyzed the control charts with those process changes. Changes in median values of outcomes in each period were compared by Kruskal-Wallis test, and proportions were compared by χ² test.

We then validated our findings from the control charts by using interrupted time series (ITS) analysis, which can distinguish change in outcome occurring because of an intervention from change that would have been expected on the basis of the trend occurring during the previous time period. To assess differences between periods, we calculated differences between the average level in each period while controlling for the trend in the baseline period.

We used QI Macros for Excel version 2015.10 (KnowWare International Inc, Denver, CO) to create and analyze control charts. All other analyses were performed by using IBM SPSS Statistics version 22.0 (IBM Corporation) and SAS software version 9.4 (SAS Institute Inc, Cary, NC).

**RESULTS**

Demographic data for infants admitted to the NICU at <1 month corrected age were similar in each period, with the exception of fewer surgical diagnoses in period 3 (Table 1).

For the primary outcome measure of number of nonindicated prescriptions per month, c-chart analysis showed a significant decrease in each postimplementation period, from 7.5 in the baseline period to 2.5 in period 2 and 0 in period 3 (Fig 3). Statistical comparison of the medians in the 3 periods (Table 2) confirmed significant differences. ITS analysis (Table 3) confirmed the significant reduction in nonindicated prescriptions in each period, revealing that after taking into account the trend toward increasing prescription of PPIs/H2RAs over time during the baseline period,
there were on average 7.9 fewer prescriptions per month in period 2 than expected and 12.8 fewer per month in period 3. As a sensitivity analysis, we also performed control charts and ITS analysis for the number of nonindicated prescriptions if medication trial prescriptions were classified as nonindicated, and the significant reduction in each period remained (data not shown).

Concurrent with the decrease in nonindicated prescriptions, the total number of PPI/H2RA prescriptions per month also decreased from 11.6 at baseline to 3.7 in the final period (Fig 4). In addition, the ratio of PPI/H2RA patient days to total patient days (which reflects the overall burden of exposure to acid-suppressing medications) decreased to less than half the baseline value (20.2% vs 44.7%, \( P < .001 \)) (Fig 5). Statistical comparison of the median values in each period confirmed significant decreases between periods (Table 2). With our ITS analysis, we confirmed the significant reduction in patient days of medication exposure but the reduction in total number of prescriptions did not reach statistical significance (Table 3).

The Pareto chart showed that before guideline implementation, acid-suppressing medications were commonly prescribed to infants

### TABLE 2 Process and Outcome Measure Results

<table>
<thead>
<tr>
<th>Measurea</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process measure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. PPI/H2RA prescriptions with completed paper-tracking form, ( N ) (percentage of PPI/H2RA prescriptions)b</td>
<td>—</td>
<td>19 (37.3%)</td>
<td>17 (77.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. nonindicated prescriptions per month, median (range)</td>
<td>7.5 (4–11)</td>
<td>2 (0–8)</td>
<td>0 (0–2)</td>
<td>.001</td>
</tr>
<tr>
<td>Total no. prescriptions per month, median (range)</td>
<td>11.5 (7–16)</td>
<td>8 (4–12)</td>
<td>2.5 (2–8)</td>
<td>.002</td>
</tr>
<tr>
<td>Patient days with PPI/H2RAs over total patient days per month, percentage (95% CI)</td>
<td>42.8% (41.3–44.3)</td>
<td>32.9% (31.6–34.3)</td>
<td>20.2% (19.9–21.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Proportion of infants &lt;1 mo corrected age who developed infection, percentage (95% CI)</td>
<td>18.1% (14.2–22.1)</td>
<td>15.7% (12.1–19.3)</td>
<td>14.3% (10.3–18.4)</td>
<td>.40</td>
</tr>
</tbody>
</table>

CI, confidence interval; —, not applicable.

*a Data are displayed as median (range) for integer data, compared by a Kruskal-Wallis test and percentage (95% CI) or \( N \) (percentage) for proportion data, compared by a \( \chi^2 \) test.

*b Process measure was only calculated for mo after implementation of the paper-tracking form in July 2015.

### TABLE 3 ITS Analysis of Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Nonindicated Prescriptions</th>
<th>Total Prescriptions</th>
<th>PPI/H2RA Patient Days per Total Patient Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline trend (slope)</td>
<td>0.3 (( P = .04 ))</td>
<td>−0.03 (( P = .26 ))</td>
<td>0.1 (( P = .87 ))</td>
</tr>
<tr>
<td>Level change from period 1 to period 2</td>
<td>−7.9 (( P &lt; .001 ))</td>
<td>−3.4 (( P = .21 ))</td>
<td>−12.8 (( P = .08 ))</td>
</tr>
<tr>
<td>Level change from period 1 to period 3</td>
<td>−12.8 (( P &lt; .001 ))</td>
<td>−7.5 (( P = .11 ))</td>
<td>−26.3 (( P = .04 ))</td>
</tr>
</tbody>
</table>

### FIGURE 3

C-chart of nonindicated prescriptions of acid-suppressing medications among infants <1 month corrected age. Triangles with a dashed line represent the number of nonindicated prescriptions under the original guideline definitions (ie, the number of infants started on a trial of acid-suppressing medications for indications not specifically covered by the guideline). CL, center line; LCL, lower control limit; UCL, upper control limit.
with surgical diagnoses while NPO, particularly through routine inclusion of H2RAs in PN (Fig 6). After our first PDSA cycle that was focused on PN, we eliminated routine use of H2RAs and virtually eliminated nonindicated H2RA use in PN, which was sustained throughout the entire project (Supplemental Fig 7). Infants with gastroschisis were also routinely prescribed acid suppression during the baseline period, which we eliminated completely (Fig 6). Improvements in prescriptions for GER and apnea and bradycardia were slower but finally decreased in period 3 after additional PDSA cycles introducing staff incentives for guideline adherence and real-time data collection on rounds.

There was a significant increase in paper-tracking form completion in period 3 (Table 2), which served as our process measure. None of the nonindicated prescriptions had a paper-tracking form filled out.

Complications associated with PPI/H2RA use were variable during each period, but showed no significant change over time (Table 2). The most common occurrence was infection, with an incidence of 14% to 18%. No infants developed necrotizing enterocolitis or fracture during or after treatment with PPIs/H2RAs. There were no cases of our balancing measure, gastrointestinal bleeding.

**DISCUSSION**

Implementation of an evidence-based guideline for use of acid-suppressing medications resulted in a significant decrease in prescription of these medications in our tertiary and quaternary NICU, particularly for conditions not supported by the guideline. We also showed a significant reduction in the exposure of infants <1 month corrected age to acid-suppressing medication, both in terms of number of prescriptions and percentage of patient days on which acid suppression was administered, after guideline implementation.

Nonindicated uses among surgical patients (gastroschisis and routine inclusion in PN for NPO infants) declined quickly after guideline implementation, suggesting that education alone was enough to change practice. Inclusion of a pediatric surgeon on the project team likely improved buy-in and uptake among the surgical providers. Improvements for medical diagnoses such as reflux and apnea and bradycardia were slower despite broad support from physicians, including the medical director of our NICU. This may have been, in part, because of lack of guideline awareness among some rotating attending physicians, and adherence improved after guideline dissemination among this group.

After guideline launch, we used several PDSA cycles to improve guideline adherence. Interventions such as including acid-suppressing medications on the nurses’ rounding sheet had limited impact, whereas the introduction of staff incentives had notable impact, which remained even after discontinuation of the incentives, indicating sustained change. Real-time data collection was key to the project’s success by allowing us to provide the staff incentives and give timely feedback to providers, and because the process of daily data collection likely also increased staff awareness of the guideline. We noted anecdotally a marked improvement in documentation of the indication for PPI/H2RA prescription throughout the postimplementation periods, suggesting increased staff awareness of the guideline and thoughtfulness about indications for use.

Responding to staff feedback and revising the guideline to include a trial of medication use for difficult cases was also instrumental in achieving 100% adherence to the guideline. The decision of staff to...
prescribe PPIs/H2RAs in these trial cases was largely claimed to be a “last resort” before more invasive treatments (such as postpyloric feeds) were pursued. We were reassured that providers did not use the trial as an excuse for liberal prescription because the burden of PPI/H2RA exposure continued to decrease in period 3. Over a 6-month period, there were only 3 cases of the trial being used, all for possible GERD: 1 of the patients had the rare diagnosis of diaphragmatic flutter and was treated long-term because of symptomatic improvement during the trial, whereas the other 2 were discharged 1 and 3 days after medication initiation (1 of whom was available for follow-up, and medication was discontinued because of ineffectiveness).

Despite the significant reduction in use of acid-suppressing medications, we did not detect any decrease in the incidence of potentially associated adverse events, including infection, necrotizing enterocolitis, or fractures. Necrotizing enterocolitis and fracture were such rare events that conclusions are limited. Infections, on the other hand, are relatively common in the NICU but are multifactorial events unlikely to be solely attributable to acid-suppressing medications.

Our project has some limitations. This intervention may not be generalizable to NICUs that care for a different patient mix (for example, nonsurgical cases or primarily inborn infants) or in which rates of PPI/H2RA use are already low; although, the baseline rate of acid-suppressing medication use and indications for prescription in our unit were remarkably similar to other published series including units with widely varying patient populations. Development of any guideline for acid-suppressing medications in neonates is limited by the poor quality of available efficacy data, and it could be argued that there are no indications for PPI/H2RA use in the NICU that are supported by high-quality evidence. Nevertheless, even with the inclusion of some controversial indications in our guideline, we were able to significantly impact prescription rates. The decline in total prescriptions paralleling the decline in nonindicated prescriptions is reassuring in that prescribers did not simply reclassify prescriptions from nonindicated to indicated conditions. In addition, although we did not see any increase in potential adverse events, continued monitoring is needed to ensure decreased PPI/H2RA use is not associated with adverse events over time. Finally, although this guideline was successful in the inpatient setting, recent evidence shows the majority of infants receiving acid-suppressing medications after NICU discharge were started on the medication as outpatients. Given the known risks of PPI/H2RA use in outpatient infant populations, addressing outpatient prescription via establishment of similar guidelines would be an important next step but was beyond the scope of our project.

CONCLUSIONS

Given the mounting evidence for potential adverse effects, acid-suppressing medications should only be prescribed to neonates after careful consideration. Implementation of an evidence-based guideline in our tertiary and quaternary NICU accompanied by leadership involvement, staff

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FIGURE 5

P-chart of burden of acid-suppressing medication exposure among infants <1 month corrected age, expressed as percentage of patient days on which infants received acid-suppressing medications. Numbers shown are the center line for each period. CL, center line; LCL, lower control limit; UCL, upper control limit.
incentives, and real-time data tracking led to excellent adherence that directly correlated with a substantial decrease in overall burden of exposure to PPI/H2RAs in our unit. This guideline could be feasibly implemented in other similar settings providing inpatient care to sick newborns.

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REFERENCES


ABBREVIATIONS

GER: gastroesophageal reflux
GERD: gastroesophageal reflux disease
H2RA: histamine-2 receptor antagonist
ITS: interrupted time series
NPO: nil per os
PDSA: plan-do-study-act
PN: parenteral nutrition
PPI: proton pump inhibitor

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