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Decreasing Inappropriate Use of Antireflux Medications by Standardizing Gastroesophageal Reflux Disease Management in NICU

Fauzia M. Shakeel, MD, CPHQ; Jacquelyn Crews, MD†; Preceous Jensen, MD*; Andrea Ritchey, RN*; Megan Allen, PharmD‡; Jazmine Mateus, MPH§; Joana Machry, MD**

Abstract

Introduction: Gastroesophageal reflux (GER) is a functional self-limiting condition in neonates. When pathologic, it is called GER disease (GERD). There are wide variations in the management of signs, symptoms, and complications associated with GERD in the neonatal intensive care unit (NICU). Evidence does not support an empiric trial of GERD medications as a diagnostic tool or therapy in premature infants. **Methods:** A multidisciplinary team developed evidence-based clinical practice guidelines (CPG) for GERD management. Process improvement included developing a GERD management algorithm, electronic order sets, and education for all providers. Multiple plan-do-study-act cycles done. **Results:** Implementation of standardized GERD management guideline, decreased the overall use of antireflux medications from baseline, 15.1%–6.8% [χ^2 (1, N = 1259) = 12.98, $P < 0.001$]. There was elimination of GERD medication use in preterm from baseline of 19.3% [χ^2 (1, N = 220) = 12.18, $P < 0.001$]. The most frequently used GERD medication was lansoprazole, with an incorrect initial dosing rate of 55.0% that deceased to zero [χ^2 (1, N = 33) = 10.73, $P = 0.001$]. Appropriate testing with PH probe with 24-hour multichannel impedance was observed (17.1%–28.0%) identifying patients with correct GERD diagnosis [χ^2 (1, N = 101) = 1.41, $P = 0.236$]. Length of stay for GERD patient's improved from a median of 89–53 days. **Conclusion:** Standardizing clinical management leads to best practices for GERD management with appropriate diagnostic testing, eliminating incorrect medication dosing, and improved patient safety with value-based outcomes. *(Pediatr Qual Saf 2021;6:e394; doi: 10.1097/pq9.0000000000000394; Published online March 10, 2021.)*

INTRODUCTION

Gastroesophageal reflux (GER) is a common functional, self-limiting condition that occurs several times a day in healthy infants, lasting less than 3 minutes, with few or no symptoms observed.[1] Within the first 2 months of life, 70%–85% of infants will have episodes of regurgitation that typically improve by 4 months of age and resolves in 95% of infants by 1 year of age.[1,2] When the condition becomes pathologic and associated with complications, it is called GER disease (GERD). In infants, GERD is defined as recurrent emesis or reflux and poor weight gain, choking, gagging, coughing, significant irritability, frequent crying, discomfort, arching, feeding aversion, or forceful vomiting of gastric contents.[3,4] Although these symptoms can be more pronounced in preterm infants based on their degree of prematurity, they usually do not represent disease; however, they mislead practitioners to prescribe antireflux medications with limited benefits and potential harm. There is evidence that antiacid medication in premature infants is associated with severe morbidities like necrotizing enterocolitis (NEC) and late-onset sepsis (LOS). The mechanism proposed is related to reduce gastric acidity, alteration within the gut microbiome, and interference with immune function leading to gastrointestinal infections in neonates.[5,6]

Also, within the preterm population where cardiorespiratory events (apnea or bradycardia, with or without the presence of desaturation)[2,7,8] are also frequent, there

*From the *Department of Neonatology, Maternal Fetal and Neonatal Institute; Johns Hopkins All Children's Hospital St. Petersburg, Fla.; †Department of Pediatrics. Johns Hopkins All Children's Hospital, St. Petersburg, Fla.; ‡Division of Pharmacy and Therapeutics, Johns Hopkins All Children's Hospital, St. Petersburg, Fla.; and §Department of Health Informatics, Johns Hopkins Children's Hospital, St. Petersburg, Fla.*

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**Corresponding author. Address: Fauzia M. Shakeel, MD, CPHQ, Johns Hopkins All Children's Hospital, Maternal Fetal and Neonatal Institute, 600 5th Street South, St. Petersburg, FL 33701*
PH: 727-767-4313; Fax: 727-767-4391
Email: fshakee1@jhmi.edu

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has been an investigation for a possible causal association between acid reflux and the cardiorespiratory events. In reality, what is known is that premature infants have nonacid or weakly acidic-reflux, rather than acid-reflux, and current causal association between GERD and apnea of prematurity remains unlikely.[9,10]

There is a lack of consensus on how best to define and diagnose GERD in neonates, especially in the preterm population. Clinicians use different strategies based on their experiences and training, resulting in a wide variation in practice. More recently, with advances in diagnostic technology, van Wijk et al[14] propose that a 24-hour pH probe with multichannel impedance (MC Impedance) be used in infants to detect acid and nonacid reflux, especially in the preterm population which has predominantly nonacid or weakly acid reflux. Currently, according to the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines, "there is no evidence to support an empiric trial of acid suppression as a diagnostic test in infants [term or preterm] where symptoms suggestive of GERD are less specific."[1] Use of medications such as H2-receptor agonists (H2RA), proton-pump inhibitors (PPIs), and prokinetics can cause subsequent community-acquired pneumonia and gastrointestinal infection.[1] Evidence also exists that discourages antiacid medication use in preterm infants due to the high risk of NEC and sepsis while offering little benefit.[15] In infants experiencing significant cardiopulmonary events or actual evidence of GERD from diagnostic testing, the use of these medications may be appropriate.

Because of a lack of evidence to support the routine use of antireflux medication in a highly vulnerable population of neonates, added to the potential for significant harm from medication side effects or inappropriate dosing, and unnecessary additional cost, we assembled a multidisciplinary team of medical professionals for a quality improvement project in an NICU.

Aims

This project aimed to decrease the inappropriate use of antireflux medications in preterm infants less than 37 weeks postmenstrual age (PMA) from 19% to 0%. We define inappropriate usage as the wrong timing of initiation, inadequate testing, and incorrect dosing of GERD medications by standardizing GERD management guidelines in preterm infants in the NICU by July 2017.

METHODS

Johns Hopkins All Children's Hospital Maternal, Fetal, and Neonatal Institute is a designated Regional Perinatal Intensive Care Center by Florida's Children Medical Services. The NICU is a 97-bed Level IV NICU, offering the highest level of care dedicated to improve newborn outcomes. A multidisciplinary group of medical professionals, including neonatologists, gastroenterologists, pediatric hospitalists, pediatric surgeons, advanced practice providers, clinical informatics specialists, and clinical pharmacists developed an evidence-based GERD clinical practice guideline (CPG) and algorithm (**see Appendix 1, Supplemental Digital Content 1**, which describes GERD Clinical practice Guidelines Algorithm, ***http://links.lww.com/PQ9/A245***). We established baseline data from 2013 before implementing the test of change. Overuse of GERD medications in NICU was identified in 2013, with small changes made in the subsequent years while preparing for this quality improvement initiative's rollout. We excluded these years before full implementation in 2017. We obtained baseline data for the 24-hour pH probe with multichannel impedance testing from procedure logs from our institution's Special Procedures Units, where these tests are performed. The CPG was developed to address the preterm population under 37 weeks gestational age at birth. We obtained baseline data evaluating the use and dosage of anti-reflux medications in all patients discharged from the NICU as well as a subset including premature infants less than 37 weeks corrected gestational age using retrospective review and analysis of electronic medical record, obtained from the pharmacy clinical surveillance tool TheraDoc (Premier, Inc., Charlotte, N.C.).

Using these baseline data, we established operational definitions for the key metrics of the initiative based on 3 elements: (1) inappropriate use of antireflux medication (patients having an inadequate evaluation and/or testing before medication treatment); (2) patients initiating medication treatment before 37 weeks PMA; or (3) patients receiving incorrect antireflux medication doses.

Study Design

The CPG provided definitions for GERD symptoms, nonpharmacological measures for neonatal patients until they reached 37 weeks PMA, including positioning, lengthening of feeds, substituting formula for milk protein intolerance for at-risk patients, and criteria for appropriate intervention and testing before initiation of antireflux medications (**see Appendix 1, Supplemental Digital Content 1**, which describes GERD Clinical practice Guidelines Algorithm, ***http://links.lww.com/PQ9/A245***).

The team used the Pareto principle to identify the single class of medication with the greatest impact as PPI, especially oral lansoprazole, which was the most commonly used medication in the NICU. We reviewed the safety and efficacy of oral lansoprazole. Multiple dosing regimens for lansoprazole have been evaluated in neonates including: (1) 0.5–1 mg/kg/dose once daily; (2) 0.2–0.3 mg/kg/dose once daily; and (3) 1.5 mg/kg/DAY divided twice daily.[16–18] The most common dosing regimen studied was 0.5–1 mg/kg once daily, which was efficacious and well-tolerated with no discontinuations. Increased intragastric pH and decreased GERD symptoms were seen with 5 days of administration.[18]

We also reviewed the pharmacokinetics of lansoprazole. The review identified patients younger than 10 weeks of age as having a higher plasma exposure and lower plasma clearance than patients older than 10 weeks.[19] Based on lansoprazole's safety and efficacy, we considered our standard correct initial dosing regimen to be 0.5–1 mg/kg/dose once daily.

Intervention

Adopting and applying the model of improvement as a core strategy for quality improvement, we used "plan, do, study, act" (PDSA) cycles after launching the initiative to achieve the goal. The primary process improvement measure was closing the providers' knowledge gap and following an evidence-based standardized GERD management algorithm. Subsequent PDSA cycles included staff education on 24-hour pH probe with multichannel impedance testing and appropriate and timely study documentation for premature infants with suspected GERD. As these processes were tested and implemented, we evaluated the longitudinal process measurement and its effect on the overall outcome.

Additional tests of change included the development of GERD education handouts for the staff and parents. These materials were kept at the bedside for education and reference. In addition to the handouts, multiple PDSA cycles were performed based on staff feedback to allow for effective implementation of the guidelines. We developed education and communication plans, with additional monthly multidisciplinary group meetings held to address deviations from the guidelines to help recognize and remove barriers. To assist providers with implementing these guidelines, we developed electronic GERD order sets for preterm infants, including appropriate testing and medication dosing of antireflux medications.

The primary outcome measure was to reduce the inappropriate use of antireflux medications in premature neonates. Data on appropriate GERD diagnostic testing (24-hour pH probe with multichannel impedance), age at initiation of antireflux medication, and medication dosing prospectively collected in all neonates admitted to the NICU. We excluded patients with surgical diagnoses such as abdominal wall defects, tracheoesophageal fistula, or congenital diaphragmatic hernia from the analysis. Secondary outcome measures included the utilization of nonpharmacological antireflux strategies and the impact on the length of stay and medication cost. We monitored all patients admitted to the NICU for formulary antireflux medication classes, including H2RA (PO ranitidine and IV famotidine), PPIs (PO lansoprazole and IV esomeprazole), and the prokinetics (erythromycin, azithromycin, and metoclopramide). The rate of inappropriate use of antireflux medications in the NICU for all neonates and those under 37 weeks PMA was monitored via annotated run chart as the interventions were implemented over time to track the primary outcome. Individual outcome data were plotted in run charts monthly to detect changes in real-time and to provide feedback to providers. Testing of the hypothesis that inappropriate usage of these medications was reduced from baseline to the aggregated last 3 months of the study were assessed using the Chi-squared test. *P* values of <0.05 were considered statistically significant. SAS 9.4 was used for statistical analysis.

RESULTS

The project evaluated a total of 526 neonates prospectively for 6 months. Following the implementation of a clinical practice guideline standardizing the evaluation and management of GER and GERD in the NICU, there was a significant reduction in the use of antireflux medications for all patients discharged from the NICU by the last quarter of the project (15.1% at baseline versus 6.8% at discharge [χ^2 (1, N = 1259) = 12.98, $P < 0.001$]) (Table 1). The use of antireflux medications in premature infants under 37 weeks PMA decreased from 19.3% at baseline to zero [χ^2 (1, N = 220) = 12.18, $P < 0.001$], eliminating its use in this highly vulnerable population by the final quarter of the project (Fig. 1). Analysis of antireflux medications by type revealed that for patients of all gestational ages there was a significant reduction in the use of H2RA from 4.2% to 1.1% [χ^2 (1, N = 279) = 6.22, $P = 0.013$] and prokinetics from 2.7% to 0% [χ^2 (1, N = 279) = 7.56, $P = 0.006$]. The overall decline in PPI use from 8.3% to 5.7% [χ^2 (1, N = 279) = 1.96, $P = 0.162$] for all gestational ages was not statistically significant. However, in the preterm population, there was an elimination of H2RA from 7.2% at baseline [χ^2 (1, N = 220) = 4.13, $P = 0.042$] to zero and PPI from 12.1% [χ^2 (1, N = 220) = 7.16, $P = 0.008$] to zero, by the last 3 months of the project. Prokinetics were not prescribed to neonates less than 37 weeks PMA at any time after the guideline initiation (Table 1).

The most prescribed antireflux medication in NICU was the PPI, lansoprazole. The incorrect initial dosing (>1 mg/kg/dose once daily) rate associated with lansoprazole was 55.0%, which fell significantly to 0% by the last quarter of the project. This difference was statistically significant [χ^2 (1, N = 33) = 10.73, $P = 0.001$] and likely a result of implementing electronic medical record order sets and provider education regarding correct dosing and the related harmful effects (Table 2).

At baseline, there were approximately 17.1% of patients with an ICD-10 diagnosis of GERD who were tested with the appropriate 24-hour pH probe with multichannel impedance. Although the appropriate testing rate increased to 28.0% during the last 3 months of the project, the difference was not statistically significant [χ^2 (1, N = 101) = 1.41, $P = 0.236$]. Use of hydrolyzed formulas in infants with a suspected GERD diagnosis increased significantly from 2.6% at baseline to 20.0% project end [χ^2 (1, N = 101) = 8.80, $P = 0.003$] (Table 3).

Balancing measures monitored for this project, included hospital length of stay, NEC, and LOS. These data were assessed at baseline and through the project end. The

Table 1. GERD Medication Rates by Gestational Age for All Antireflux Medications Combined and Individually

	Baseline		Project Final Quarter		Chi-squared Test Results		
Group	Total Patients	GERD Med Rate (No. Given GERD Med)	Total Patients	GERD Med Rate (No. Given GERD Med)	df	χ^2	*P*
All GA	980	15.1% (148)	279	6.8% (19)	1	12.98	<0.001*
CGA < 37 weeks PMA	166	19.3% (32)	54	0% (0)	1	12.18	<0.001*
H2RA	166	7.2% (12)	54	0% (0)	1	4.13	0.042*
PPI	166	12.1% (20)	54	0% (0)	1	7.16	0.008*
Prokinetics	166	0% (0)	54	0% (0)	—	—	—

Implementation of standardized GERD management in the NICU decreased usage of GERD medications in patients of all gestational ages and eliminated the use of these medications in preterm neonates. Usage of H2RA, PPI and prokinetics anti-reflux medications in patients under 37 weeks corrected gestational ages was eliminated in preterm neonates.
*Statistically significant difference at alpha = 0.05.
CGA, corrected gestational age at time of medication administration; GA, gestational age.

median length of hospital stay fell from 89 to 53 days for all NICU patients with an ICD-10 GERD diagnosis, though it is unclear if this was a causal association with the project intervention.

NEC and LOS remained low at 3.2% and 4.0%, respectively. After implementing the GERD management guidelines in the NICU, there was a significant reduction in anti-reflux medication use for all gestational ages.

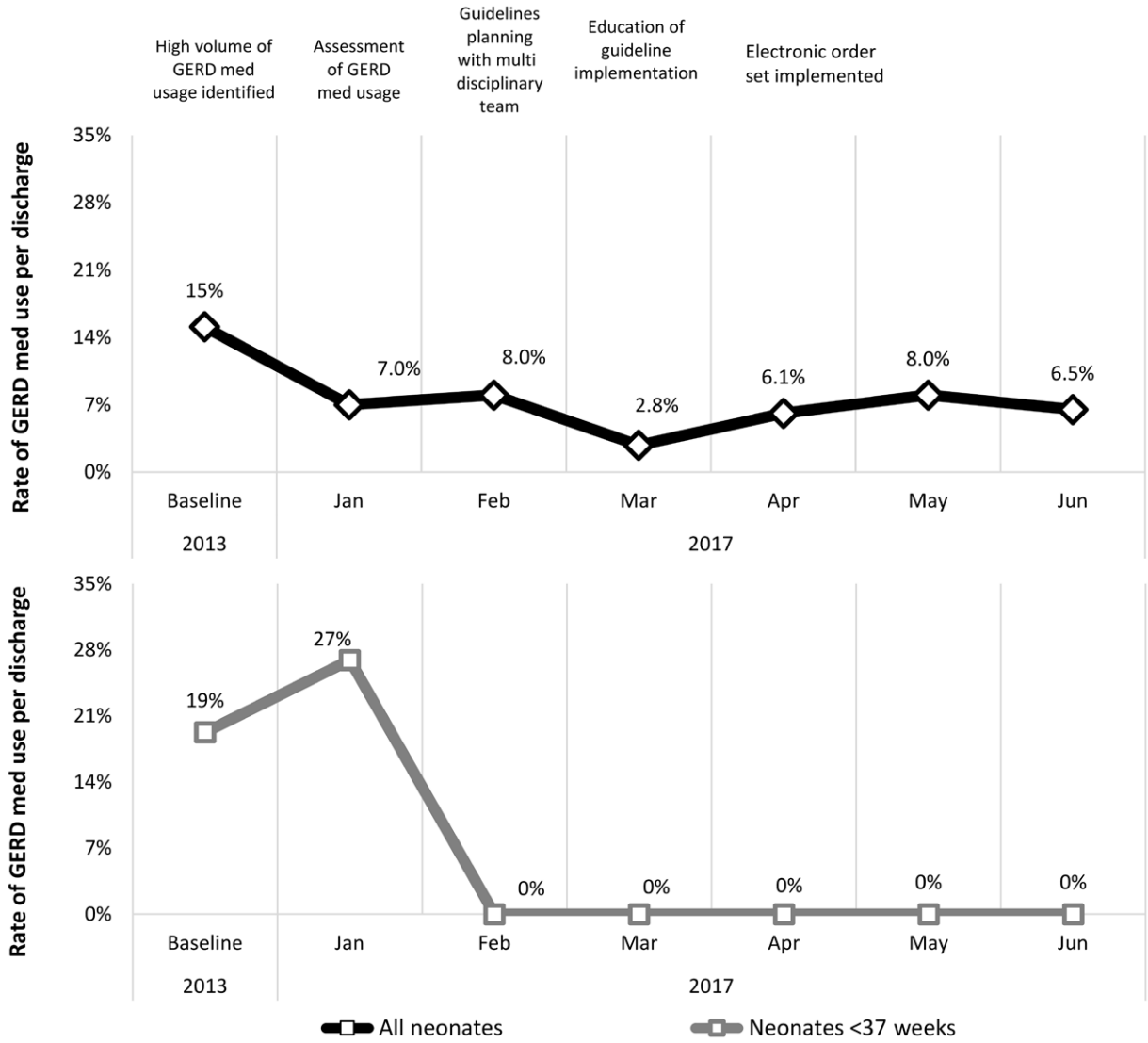

Fig. 1. Rate of GERD medication usage by NICU discharge (all neonates and neonates < 37 weeks PMA**) baseline and with project implementation. ** No special significance. It was used in data for separating term and those less than 37 weeks PMA.

Table 2. Lansoprazole (PPI) GERD Medication Incorrect Dosing Rates for All Gestational Ages

	Baseline		Project Final Quarter		Chi-squared Test Results		
GERD Medication	Total Patients	GERD Med Rate (No. given GERD Med)	Total Patients	GERD Med Rate (No. given GERD Med)	df	χ^2	*P*
PPI	20	55.0% (11)	13	0% (0)	1	10.73	0.001*

Implementation of standardized GERD management in the NICU eliminated incorrect dosing of the PPI lansoprazole during the last quarter of the project for neonates of all gestational ages.
*Statistically significant difference at alpha = 0.05.

Table 3. PH Impedance Probe Testing and Hydrolyzed Formula Usage

	Baseline		Project Final Quarter		Chi-squared Test Results		
GERD Medication	Total Patients	GERD Med Rate (No. given GERD Med)	Total Patients	GERD Med Rate (No. given GERD Med)	df	χ^2	*P*
pH probe	76	17.1% (13)	25	28.0% (7)	1	1.41	0.236
Hydrolyzed formula	76	2.6% (2)	25	20.0% (5)	1	8.80	0.003*

Use of pH probe impedance testing and hydrolyzed formula use in patients with GERD diagnosis increased by the last quarter of the project.
*Statistically significant difference at alpha = 0.05.

DISCUSSION

Implementing standardized clinical practice guidelines diagnosing and managing GERD in preterm neonates admitted to a busy level IV NICU resulted in an overall significant decrease of inappropriate use of GERD medications in neonates. The project, which primarily focused on an extensive education process to medical providers, staff, and parents, addressing knowledge gaps in diagnosing and managing GERD in neonates, significantly impacted outcomes for a highly vulnerable neonatal population. The quality initiative resulted in a nearly 55% reduction overall in antiacid medication use in NICU patients.

Although lansoprazole is well tolerated, it is not without adverse effects. In one study, 42% of patients experienced at least one adverse drug event with one incident of anemia, one incident of flushing, and one incident of increased aspartate aminotransferase.[4] Another study identified 62% of treatment-emergent adverse events in the lansoprazole group versus 46% in the control group.[2] Lower respiratory tract infections occurred significantly more frequently in the lansoprazole group compared with the placebo group.[2] Through appropriate dosing of lansoprazole, treatment-emergent adverse events of lansoprazole may have contributed to the decreased length of stay.

Over the past decade, there has been an increased awareness in the literature about the overuse of antiacid medications among infants. One large study of the US healthcare databases showed that from 1999 to 2004, there was a >7-fold increase in PPI prescriptions. Approximately, 50% of the infants started taking a PPI before 4 months of age. Despite being on anti-GERD medications, the majority of patients were not evaluated with appropriate diagnostic testing.[20] Data from the National Institute of Child Health and Human Development identified that 25% of extremely low birth weight infants admitted to network centers were discharged home on GER medications.[21] These data exposed the national utilization of medications with potentially harmful side effects without evidence in medical science to support its use for the neonatal population.

Empirical pharmacotherapy for GER in neonates interferes with the normal physiological microbiome, enhancing the growth of pathogens and increasing the risk for NEC and LOS. Although NEC and increased LOS can be multifactorial in this patient population, bacterial colonization and translocation are important mechanisms in NECs pathogenesis. For this project's duration, we monitored our overall rate of NEC and LOS as secondary outcomes and hospital length of stay as a balancing measure.

The CPG algorithm standardized the timing of GERD diagnostic evaluation once premature infants achieved postmenstrual age greater than or equal to 37 weeks. The recommended test was a 24-hour PH probe with a multichannel impedance probe with an appropriate nursing correlation of observed symptoms with the probe readings. Before 37 weeks with suspected GERD, the algorithm guided the primary caregiver teams to prescribe nonpharmacologic measures for reflux management such as positioning,[22] lengthening gavage feeding infusion times, utilization of transpyloric feeding,[23] and using hydrolyzed formulas before the provision of pharmacotherapy. Extensively hydrolyzed protein formulas reduce gastrointestinal transit time and symptoms in term infants with symptomatic GER[24]; however, there is evidence suggesting a potential overlap of symptoms of cow milk protein allergy and those attributed to GER, including vomiting, failure to thrive, and irritability.[25] Also, in small studies of preterm infants, extensively hydrolyzed protein formula compared with standard formula or human milk resulted in fewer reflux episodes as measured by multichannel impedance testing and pH study. It is unclear what role cow's milk protein allergy may play in preterm infants with signs of GER. Thus, a trial of

extensively hydrolyzed protein-based formula is reasonable in age-appropriate preterm infants corrected to 37 weeks for 1–2 weeks without evidence of metabolic bone disease, before medication use.[11–13,25]

The CPG algorithm also required proof of acid reflux above normal levels for age (reflux index > 4), via a 24-hour PH probe with multichannel impedance studies before anti-reflux medications administration. If pathologic acid reflux is identified, PPIs are recommended over other medication classes, leading to decreased usage of H2RA and prokinetics. The algorithm did not allow for prokinetics at any age because of the side effect profile and FDA safety warnings without evidence proven efficacy associated with that medication class.

Hospital length of stay for patients with the GERD diagnosis decreased from 89 to 53 days, and we saw a substantial impact on cost savings from decreased use in PPI. Comparison of lansoprazole use before and during the project showed a cost savings of 93.2% for all gestational ages and 85.4% for preterm neonates less than 37 weeks PMA. Cost savings were calculated based on a reduction of medication use only.

Appropriate conservative and expectant management of GER symptoms, until patients were 37 weeks, did not delay diagnosis nor increase the length of stay. Frequently, cardiorespiratory events (apnea, bradycardia, and desaturation) commonly present in premature infants are attributed to GERD. Currently, the literature does not support a causal association between GERD and cardiorespiratory events.[3,10,26] After this project, patients who had longer hospitalizations due to unresolved cardiorespiratory events may be no longer mislabeled with GERD. Also, providing education to caregivers on physiologic reflux versus pathological reflux may have affected evaluation for discharge readiness and parental reassurance. Accurate conclusions about the shorter length of stay for patients with GERD diagnosis after the project would require further investigation. Comparison of lansoprazole use before and during the project showed a cost savings of 93.2% for all gestational ages and 85.4% for preterm neonates less than 37 weeks PMA.

The project has several limitations. We conducted this study at a single major referral center. However, the interventions improved the inappropriate use and cost of antiacid medication. An initial improvement in antireflux medication usage occurred during the assessment and planning phase of this study, which, while not specifically studied, may have been related to a Hawthorne-like effect as providers learned about the deviation from current literature suggesting avoidance of empiric use of these medications and dedicated increased attention to avoid this regimen. Decreased medication use improved further during the implementation phase, illustrating a meaningful intervention. We were not able to demonstrate an impact on clinical outcomes associated with medication side effects. Despite the CPG algorithm recommending non-pharmacologic measures to address GER, there is no data on how effective those measures were to alleviate the reported symptoms. Nonetheless, substantial evidence has been published within the last decade on potential harmful side effects with anti-reflux medication use in the preterm population.[27] We caution clinicians about prescribing those medications without a clear indication of pathologic reflux. Efforts to limit inappropriate use of antireflux medication have the potential for a significant impact on patient safety and clinical outcomes.

CONCLUSIONS

In a high-risk population of preterm infants, evidence-based clinical practice guidelines provided a framework for standardized diagnosis and management of GERD with the consequent decrease in inappropriate use of antireflux medications and promoting a decrease in the use of potentially harmful antireflux medications in NICU. These guidelines are simple to implement and clinically adaptable in any hospital with benefits to patient outcomes and healthcare costs.

DISCLOSURE

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

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