Issue 2 • Volume 5

Individual QI projects from single institutions

OPEN

Screening With Reticulocyte Hemoglobin Increased Iron Sufficiency Among NICU Patients

Sarah U. Morton, MD, PhD; Jenny Chan Yuen, MSPH*; Henry A. Feldman, PhD*; Emily Hashim, MS, RD, LDN†; Coral Rudie, RD, LDN†; Kristen E. Lindamood, NNP*; Daniel Caughey, BA*; Mark Moline, RN*; Jessica K. Sims, BS*; Martha C. Sola-Visner, MD*; Kristen T. Leeman, MD**

ABSTRACT

Introduction: To increase the rate of iron sufficiency among neonatal intensive care unit (NICU) patients from 16% to >35% within 12 months of implementing standardized assessment of reticulocyte hemoglobin (retHE). **Methods:** We implemented a quality improvement (QI) study to improve iron sufficiency in our out-born level III/IV NICU. We screened 2,062 admissions, of which 622 were eligible based on feeding status at discharge. QI interventions included educational efforts and guideline implementation. Our primary outcome measure was the percentage of patients with their discharge retHE measure within the normal range. We also tracked the process measure of the number of retHE tests performed and a balancing measure of the incidence of elevated retHE among patients receiving iron supplementation. Statistical process control (SPC) charts assessed for special cause variation. **Results:** The percentage of patients with a retHe within the normal range was significantly increased from a mean of 20% to 39% on SPC chart analysis. We measured significantly more retHE values after guideline implementation (11/mo to 24/mo) and found no cases of elevated retHE among patients receiving iron supplementation. **Conclusions:** After the implementation of a standardized guideline, a higher rate of iron sufficiency was found in NICU patients at discharge. This work is generalizable to neonatal populations with the potential for a significant impact on clinical practice. *(Pediatr Qual Saf 2020;2:e258; doi: 10.1097/pq9.0000000000000258; Published online February 13, 2020.)*

INTRODUCTION

Optimal early nutrition is essential to support the rapid growth and development of neonates, especially those born preterm or with serious medical conditions.[1–3] Providing nutrition adequate to support optimal growth is a major clinical challenge. The majority of iron transfer to the fetus occurs in the third trimester, placing preterm infants at increased risk for iron deficiency.[4] Other populations, such as small-for-gestational-age infants and infants of diabetic mothers, have a significant risk of iron insufficiency.[5,6] There is increasing awareness that iron deficiency, even in the absence of anemia, can have negative health and neurodevelopmental effects.[7–9] Previous studies have demonstrated that reticulocyte hemoglobin (retHE) is a reliable and sensitive measure of iron status,[10–13] and is the recommended screening test from the American Academy of Pediatrics.[14] Recent animal studies have shown it to be the most sensitive hematological marker of brain iron deficiency.[15] Currently, the American Academy of Pediatrics recommends routine supplementation in preterm infants but delays supplementation until 4 months for breastfed term infants.[14] Anemia is a late finding in iron deficiency, and identification of an early marker of low iron status could lead to earlier treatment and optimization of supplementation. We aimed to increase the rate of neonatal intensive care unit (NICU) patient iron sufficiency by instituting a guideline focused on retHE-driven initiation and titration of iron supplementation.

To determine if screening with retHE among NICU patients can improve iron sufficiency at NICU discharge, we tested and implemented standardized guidelines for measurement of retHE and titration of supplemental iron among patients receiving enteral feedings. Within 12 months of implementation, our goals were to (1) double the assessment of iron deficiency by retHE among NICU patients from 10/mo to >20/mo; and (2) increase

*From the *Division of Newborn Medicine, Boston Children's Hospital, Boston, Mass.; and †Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Boston Mass.*

**Corresponding author. Address: Sarah U. Morton, MD, PhD, Division of Newborn Medicine, 300 Longwood Ave, Boston MA 02115*
PH: 617-355-0548; Fax: 617-730-0486
Email: sarah.morton@childrens.harvard.edu

To cite: Morton SU, Yuen JC, Feldman HA, Hashim E, Rudie C, Lindamood KE, Caughey D, Moline M, Sims JK, Sola-Visner MC, Leeman KT. Screening With Reticulocyte Hemoglobin Increased Iron Sufficiency Among NICU Patients. Pediatr Qual Saf 2020;2:e258.

Received for publication August 15, 2019; Accepted January 17, 2020.

Published online February 13, 2020

DOI: 10.1097/pq9.0000000000000258

the percentage of enterally fed patients with retHE values within normal range at time of discharge from 16% to >35%.

METHODS

Setting

Boston Children's Hospital (BCH) has an urban 24-bed level III/IV NICU and cares for ~650 patients annually, with 80% admitted to the medical team, and 20% admitted to the surgical team. All patients are out-born infants up to 6 months of corrected post-menstrual age with complex medical and surgical conditions. All infants are cared for by a multidisciplinary team that may include neonatologists, general surgeons, neonatal and surgical fellows, neonatal nurse practitioners, neonatal nurses, respiratory therapists, nutritionists, lactation consultants, social workers, pharmacists, and child life specialists.

Local Problem

Before our project start, substantial variation in clinical practice existed regarding the assessment and treatment of iron deficiency. The clinical team typically started patients on iron supplementation based on an assessment of patient gestational and chronological age, feeding type, clinical status, and laboratory testing. Standard practice before the guideline included measurement of retHE values as part of a reticulocyte panel if ordered by providers, but no systematic guidelines for response existed. The retHE is a parameter generated by Sysmex Hematology Analyzers (Sysmex America, Inc. Lincolnshire, Ill.). Other devices can also generate similar parameters, such as retHE content [CHr] by Bayer ADVIA, *Bayer* Diagnostics, Tarrytown, N.Y.

The multidisciplinary team used the IHI Model for Improvement to iteratively test clinical practice changes outlined in the guideline.[16] We generated a key driver diagram (Fig. 1) to highlight drivers and change concepts to focus on to drive change. The top identified barriers to achieving high rates of compliance included physician teams that rotate every 2 weeks and different levels of knowledge about the diagnosis and management of iron deficiency.

Goals and Measures

Our overall goal was to, within 12 months of implementation, (1) double the assessment of iron deficiency by retHE among NICU patients from 10/mo to >20/mo and (2) increase the percentage of enterally fed patients with retHE values within normal range at time of discharge from 16% to >35%. We followed cases of elevated retHE values as a balancing measure. SQUIRE 2.0 guidelines[17] were used as applicable when drafting the article.

Quality Improvement (QI) Phase 1: Guideline Development

A multidisciplinary team was established and developed a guideline for standardized iron deficiency screening

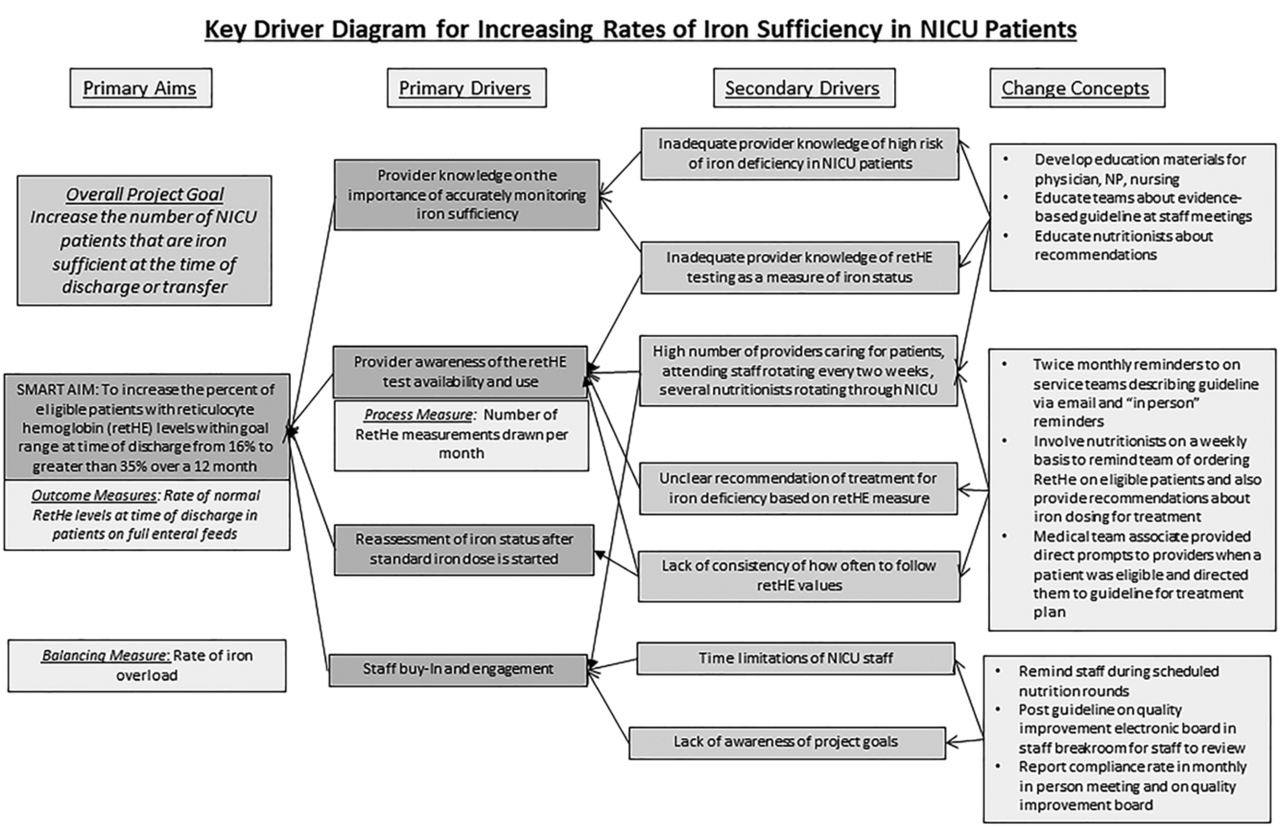

Fig. 1. Key driver diagram detailing aims, drivers, and concepts for the project.

and iron supplementation in the NICU using published evidence (Fig. 2). The team consisted of neonatologists, a pediatric gastroenterologist, a neonatal nurse practitioner, and registered dietitians. Given our complex and heterogeneous patient population with many inflammatory conditions, guideline development, testing, and implementation included consideration of barriers to applying other measures of iron deficiency, such as ferritin. NICU clinicians and relevant departments reviewed the guideline to provide comments and suggestions, including representatives from Laboratory Medicine and then approved by a multidisciplinary leadership committee. The final screening protocol was tested on a small scale and then disseminated to all NICU care providers and implemented on 1 July 2017. Key practice changes under the new guideline included (1) establishment of recommendation for routine measurement of retHE among patients receiving full feeds; (2) recommended initiation of standard iron doses for eligible patients; (3) standardized timing of reassessment of retHE during admission; and (4) standard advancement of iron supplementation in response to low retHE. Absolute contraindications to inclusion were patients not receiving enteral feeding. We targeted these guidelines to improve provider knowledge about the diagnosis and management of iron deficiency.

QI Phase 2: Iterative Change

We collected baseline data 24 months before initiation of PDSA cycles and 20 months after project start and introduction of the guideline. All patients who were admitted were screened for inclusion. We excluded patients who were not receiving enteral feedings or who were admitted for <7 days. Through direct observation and query of the care team, we obtained qualitative data regarding the utility and limitations of the interventions and incorporated these findings into PDSA cycles. Starting in May 2017, we piloted the guideline with the on-service care team. We used ongoing analysis of data regarding retHE measurements and staff feedback to develop interventions for further tests of change and refine the guideline. After the guideline was fully tested under various conditions and refined, we implemented the following: (1) daily education during patient care rounds in July 2017; (2) broad circulation of an email educational summary with the major goals and recommendations of the guideline to faculty, fellows and nurses in September 2017; (3) sharing of interval results at faculty meetings in October 2017 and January 2018; and (4) providing of patient-specific reminders for February 2018. Monthly emails to refresh knowledge of the guideline followed the first email in September 2017 to address the rotation of physician teams.

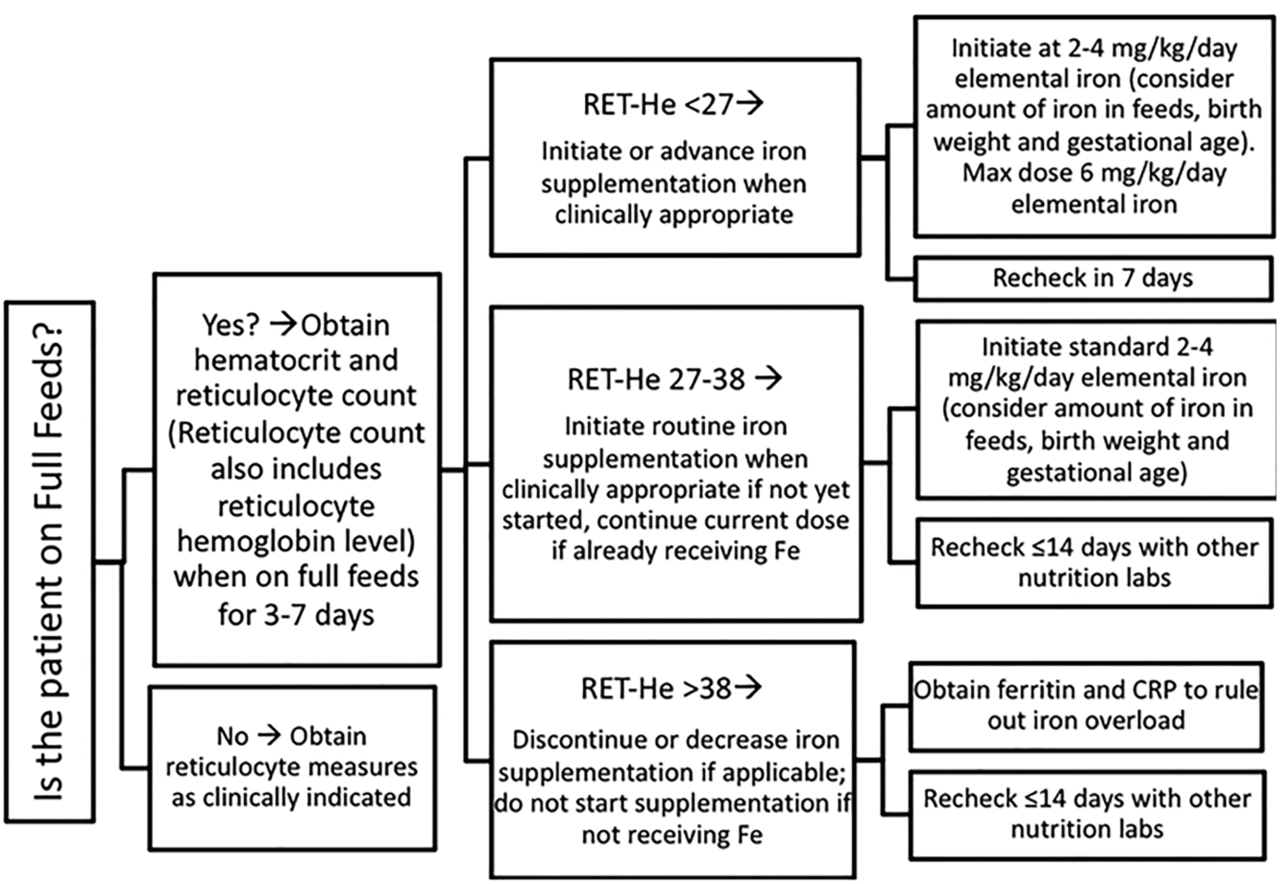

Fig. 2. Guideline for assessment and management of iron status in NICU patients.

Measures

Our main outcome measure was the percentage of patients receiving enteral feeds with retHE within the normal range at the time of discharge. Our process measure was the number of monthly retHE measures. The balancing measure was the incidence of elevated retHE values in patients receiving iron supplementation. These data were collected from time-stamped electronic health records. Data regarding the length of stay and type of feed at discharge were extracted from the BCH NICU database, which is maintained by a dedicated data coordinator who prospectively enters patient demographic and clinical data. Measures extracted from the database included length of stay defined as the number of calendar days from admission to discharge from the NICU and enteral feeding status at the time of discharge from the NICU.

Analysis

To determine if special cause variation was found during the project period, we used statistical process control (SPC) charts generated with SQCPack7 software (PQ Systems, Dayton, Ohio)[18] to make c- and p-charts. Patient characteristics before and after guideline implementation periods were compared by *t* test for continuous variables and Fisher's exact test for categorical variables. Red-cell measures were compared across 3 RetHE categories (below, within, or above normal range) by 1-way analysis of variance and by analysis of covariance adjusting for age and sex. Statistical analyses were performed in SAS (version 9.4, Cary, N.C.) with $P < 0.05$ as the criterion for statistical significance.

Ethical Considerations

The preparation of guidelines for patient care within the NICU is handled by multidisciplinary teams and incorporates evidence-based medicine, feedback from local providers, and involvement of relevant consultant services. Institutional Review Board approval was obtained for this QI project.

RESULTS

Sample

During the 44-month study period, there were 2,062 admissions, of which 626 (30%) were eligible for the guideline recommendations (Table 1) based on receiving enteral feedings and admissions of ≥7 days. Of the 1,436 admissions excluded from the study across both periods, 1,011 admissions (70%) were excluded due to admission <7 days, 157 (11%) because they were not receiving enteral feeds at

Table 1. Pre- and Post-Guideline Patient Characteristics and Clinical Variables

	Pre-guideline (7/20/2015–6/30/2017)	Post-guideline (7/1/2017–3/8/2019)	
	N		
Patients	306	238	
Admissions	350	272	
Laboratory values			
Hematocrit	1,606	1,856	
Mean corpuscular volume	1,584	1,836	
Reticulocyte percentage	175	301	
	Median(minimum–maximum); N(%); or Mean ± SD (minimum–maximum)		*P**
Gestational age, weeks	36.0 (23.1–42.1)	36.0 (23.0–42.0)	0.61
<28	31 (10)	38 (16)	0.07
28–31	29 (9)	26 (11)	
32–37	125 (41)	75 (32)	
>37	121 (40)	99 (42)	
Birth weight, grams	2,381 ± 1,045 (380–5,020)	2,301 ± 1,085 (370–4,820)	0.40
<1,500	62 (20)	66 (28)	0.02
1,500–2,500	112 (37)	63 (26)	
>2,500	132 (43)	109 (46)	
Sex			0.38
Male	173 (57)	144 (61)	
Female	133 (43)	94 (40)	
Duration of admission, days	13 (7–165)	14 (7–225)	0.25
Primary gastrointestinal diagnosis	71 (20)	60 (22)	0.62
Admission service			0.15
Medical	278 (79)	202 (74)	
Surgical	72 (21)	70 (26)	
Feeding at discharge, all admissions			0.43
Human milk only	59 (17)	48 (18)	
Human + fortifier or formula	158 (45)	109 (40)	
Formula only	133 (38)	115 (42)	
Feeding at discharge, admissions with ≥ 1 Ret-He			0.63
Human milk only	6 (7)	12 (9)	
Human + fortifier or formula	42 (46)	52 (40)	
Formula only	44 (48)	66 (51)	
Feeding at discharge, admissions with no Ret-He			0.48
Human milk only	53 (21)	36 (25)	
Human + fortifier or formula	116 (45)	57 (40)	
Formula only	89 (35)	49 (35)	

*Comparing medians by Wilcoxon rank-sum test; percentages by Fisher's exact text, or means by Student *t* test.

Table 2. Association of retHE and Other Red Blood Cell Measures

	retHE		
	Low (<27 pg)	Normal (27–38 pg)	
	N (%)		*P**
Values	99 (22)	358 (78)	
	Mean ± SD		
retHE, pg	25.3 ± 1.9	31.3 ± 2.3	<0.0001
Hematocrit, %	29.5 ± 5.1	31.0 ± 5.5	0.02
Mean corpuscular volume, fL	88.6 ± 6.7	90.6 ± 6.4	0.008
Reticulocyte %	5.0 ± 3.1	3.8 ± 2.7	0.0006

*Testing for equal means across retHE categories by independent-sample *t* test.

the time of discharge, and 268 (19%) due to both exclusion criteria. Three patients had admissions both pre- and post-guideline; we discarded their 4 pre-guideline admissions, leaving a sample of 622 admissions for analysis.

Demographic data on patients from the pre-guideline and post-guideline periods are summarized in Table 1. The distributions of gestational age, birth weight, sex, length of stay, and proportion with a gastrointestinal or surgical diagnosis were similar between the 2 study periods, with 40%–50% of patients having a birthweight of >2,500g. The feeding at discharge did not differ between the study periods.

Characteristics of RetHE Values in NICU Patients

Normal range retHE was defined as 27–38 pg based on published literature and expert consensus.[13,18–20] During the study period, there were a total of 457 retHE measurements obtained during 208 of the 622 admissions, and 99 (22%) values were lower than the normal range indicating iron deficiency (Table 2). The mean value for the overall cohort was 30.0 ± 3.3 pg (mean ± SD). None of the RetHE values were above the normal range in the eligible sample. Hematocrit, MCV, and reticulocyte percentage were all significantly different between the groups. Compared with patients with normal range retHE, those with low retHE values had lower hematocrits (–1.5 ± 0.6%, difference ± SE; *P* = 0.02), lower MCV (–2.0 ± 0.8 fL, *P* = 0.008), and higher reticulocyte percentage (+1.1 ± 0.3%, *P* = 0.0006). The association between retHE values

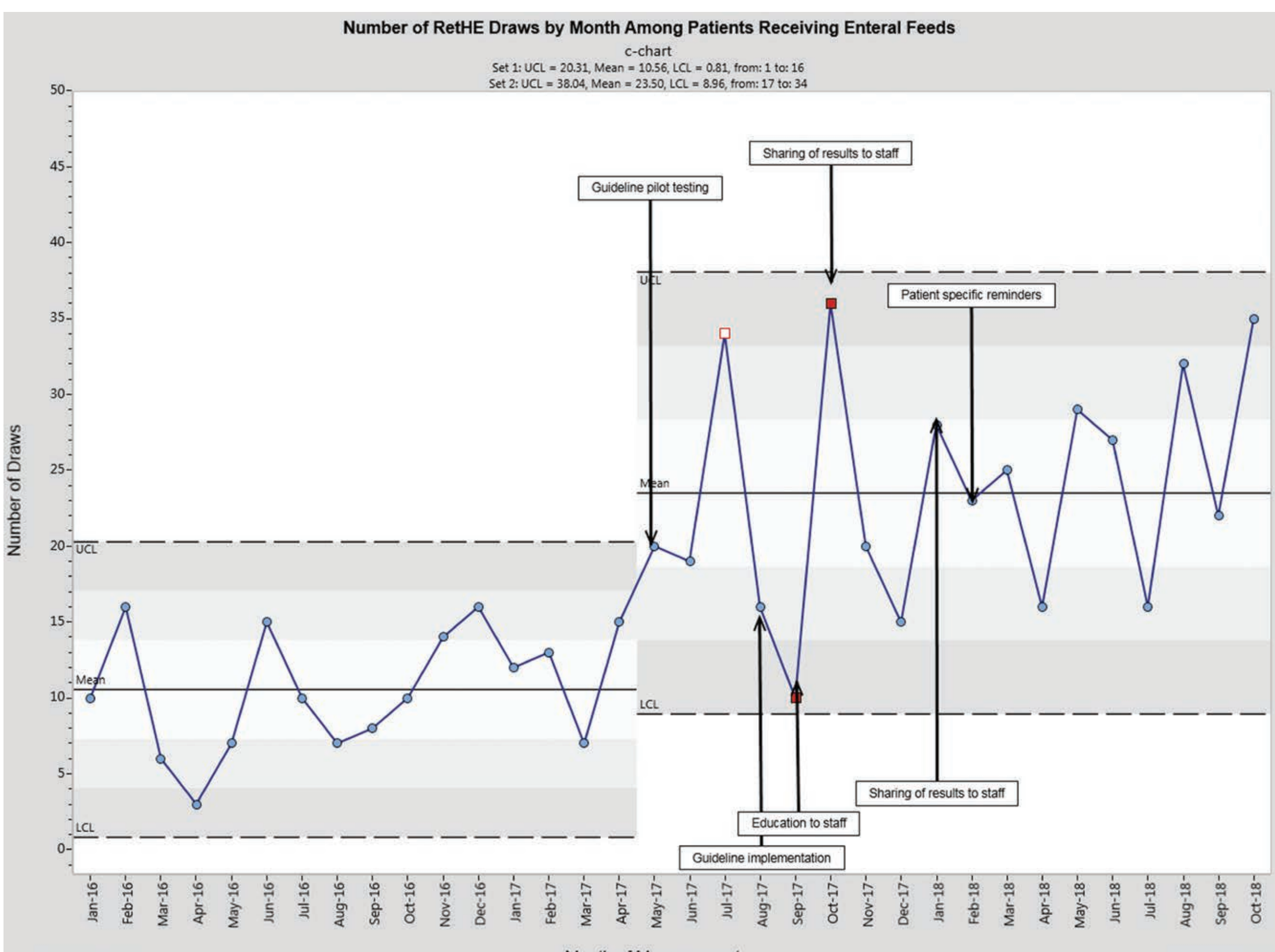

Fig. 3. SPC c chart demonstrating a significant increase in the number of retHE measurements per month that starts at the time of guideline pilot testing (process measure). Centerline shifts were determined using the rule requiring 10 of 11 points above or below the centerline.

and other red blood cell measures remained strong after adjustment for sex or age, despite lower MCV and lower reticulocyte percentage being associated with higher chronological age (decrease of 1.4 ± 0.2 fL for every 30 days, estimate ± SE, $P < 0.0001$; decrease of 0.19 ± 0.08% for every 30 days, $P = 0.02$, respectively).

Increase in RetHE Measurement After Guideline

Analysis of our process measure showed a sharp increase in the number of RetHE measurements obtained occurred following the implementation of the guideline. SPC c-chart analysis for this process measure showed special cause variation and sustained change, with a significant increase in the mean number of draws from 11 draws/mo pre-intervention to 24 draws/mo post-intervention (Fig. 3).

More Patients With RetHE Values Within Normal Range After Guideline

The mean percentage of eligible patients with retHE values within the normal range at discharge significantly improved from 20% to 39% post-guideline implementation, as shown by a shift in the mean on SPC p-chart analysis (Fig. 4), exceeding our outcome goal.

retHE Trends in Individual Patients

Overall, among the 57 low retHE values that had repeat measures from the same admission, 28 (49%) were within the normal range on the next measure, indicating iron sufficiency. Of the 192 normal range retHE values that had repeat measures, 168 (88%) remained within the normal range. Twenty patients had low retHE at least once during admission but achieved a normal range retHE at the time of discharge, of which 16 (75%) occurred during the post-guideline period. Eighteen (90%) of patients with retHE values in the normal range after a low measurement received supplemental iron per guidelines. A small number of patients (n = 12) had a retHE normal range measure at least once during admission but then had low retHE at discharge, of which 8 (67%) were in the post-guideline period. Three (25%) of those low measurements occurred when the infant had a period of all enteral feedings and supplements being held for clinical reasons. Then supplements were properly restarted when

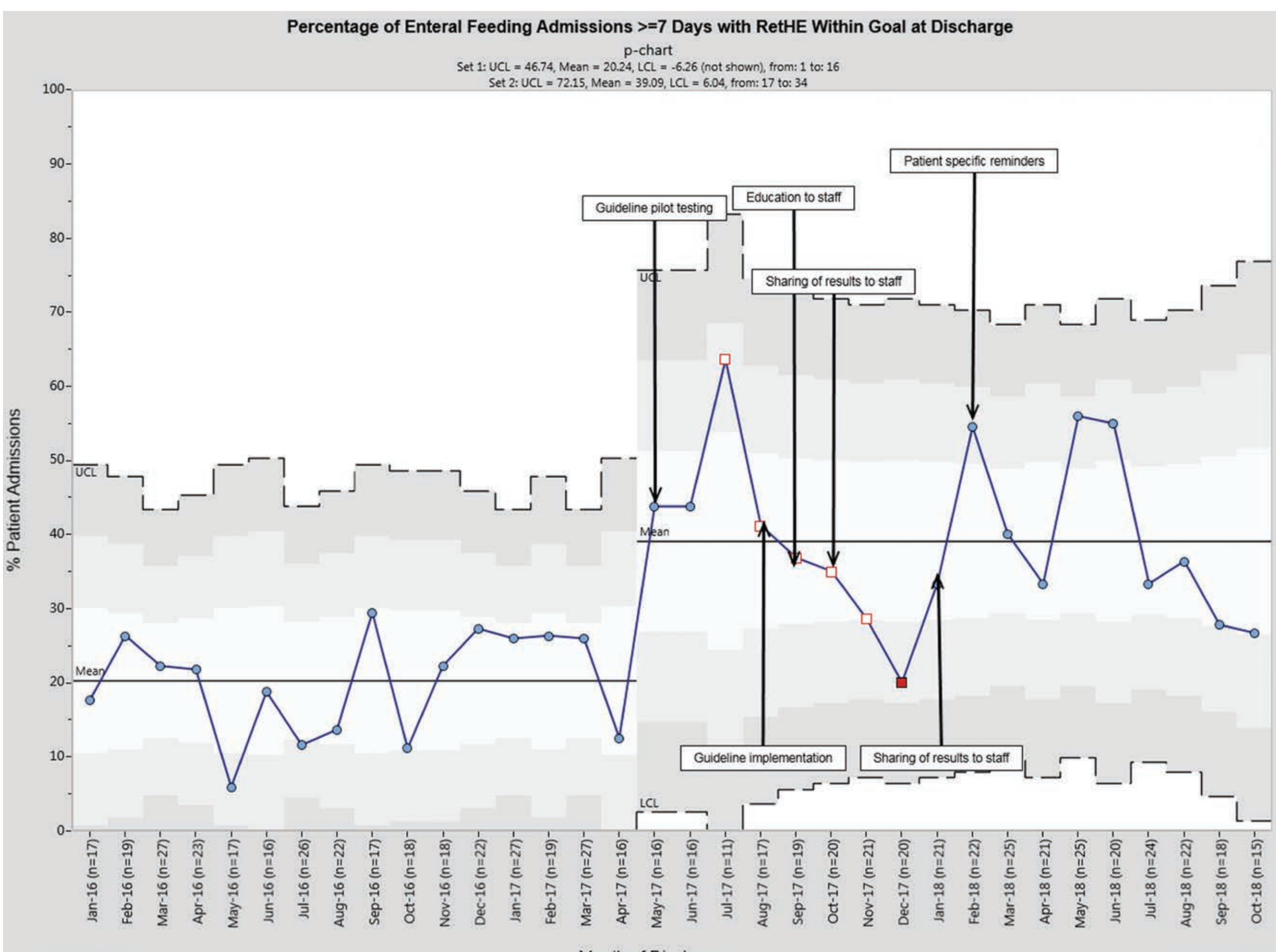

Fig. 4. SPC p chart showing a significant increase in the percentage of eligible patients with retHE within the normal range at the time of discharge after project initiation (outcome measure). Centerline shifts were determined using the rule requiring 10 of 11 points above or below the centerline.

able. All 12 infants either initiated iron supplementation or had their doses increased in response to the low retHE value but did not have a follow-up value before discharge.

DISCUSSION

Our study adds to the knowledge of iron supplementation practices in NICUs by extending beyond basic measures of iron deficiency such as ferritin and hemoglobin to include the use of the retHE measurement. Consistent with previous cohorts, in our heterogeneous NICU population, there was a strong correlation between retHE values and signs of anemia, such as elevated reticulocyte count, as well as lower hemoglobin and MCV.[10,12,13,19,21–23] We found that implementation of an iron supplementation guideline providing evidence-based recommendations for the measurement of retHE and supplementation of iron was followed by an increase of >2-fold in the percentage of patients discharged with retHE within the normal range. Our guideline successfully and significantly increased the measurement of retHE and subsequently led to an increased proportion of iron sufficient patients being discharged from the NICU. Importantly, there were no cases of excessive iron among our study cohort.

Study limitations include the single-center design and a modest number of patients included. Because we collected limited covariate data, we were unable to assess whether differences in the pre- and post-guideline groups, such as the severity of illness, could have explained the level of guideline adherence. Though we only achieved a 39% percentage of eligible patients with a normal range of retHE values, it may be that the achievable rate of iron sufficiency is relatively low in our highly complex patient population due to severity of illness, frequent needs for periods of parenteral nutrition, and ongoing phlebotomy. We note that many patients persisted in having low retHE values despite being on maximum recommended iron supplementation, pointing to an underlying etiology for iron deficiency not remedied by supplementation alone. Given the high incidence of inflammatory conditions, particularly bronchopulmonary dysplasia and short bowel syndrome, among the subset of patients with iron-refractory iron deficiency, those individuals may have increased hepcidin levels leading to iron trapping within macrophages.[24,25] Although most birth hospitals were routinely practicing delayed cord clamping, we were unable to compare rates of delayed cord clamping practice pre and post-guideline, which could affect the initial iron status of infants. Also, many patients were on full enteral feeds or standard iron supplementation for limited periods before discharge, which may lead to a delay in iron sufficiency; if retHE levels were followed after NICU discharge, the rate of iron sufficiency might be even higher than measured in our study. With this in mind, the iron status of our NICU patients at discharge, as measured by retHE, was communicated to primary care pediatricians to improve post-discharge treatment and monitoring of iron deficiency. Further work focused on decreasing the percentage of patients with iron deficiency at the time of discharge is an important area of investigation.

CONCLUDING SUMMARY

Our data show that implementation of an iron supplementation guideline utilizing retHE values can improve iron sufficiency, even for heterogeneous out-born NICU patient populations.

DISCLOSURE

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

REFERENCES

1. Bloom BT, Mulligan J, Arnold C, et al. Improving growth of very low birth weight infants in the first 28 days. *Pediatrics*. 2003;112(1 Pt 1):8–14.
2. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. *Pediatrics*. 2003;111(5 Pt 1):986–990.
3. Keunen K, van Elburg RM, van Bel F, et al. Impact of nutrition on brain development and its neuroprotective implications following preterm birth. *Pediatr Res*. 2015;77:148–155.
4. Kling PJ, Coe CL. Iron homeostasis in pregnancy, the fetus, and the neonate. *Neoreviews*. 2016;17(11):e657–e664.
5. MacQueen BC, Baer VL, Scott DM, et al. Iron supplements for infants at risk for iron deficiency. *Glob Pediatr Health*. 2017;4:2333794X17703836.
6. MacQueen BC, Christensen RD, Ward DM, et al. The iron status at birth of neonates with risk factors for developing iron deficiency: a pilot study. *J Perinatol*. 2017;37(4):436–440.
7. Angulo-Barroso RM, Li M, Santos DCC, et al. Iron supplementation in pregnancy or infancy and motor development: a Randomized Controlled Trial. *Pediatrics*. 2016;137(4):e20153547
8. Doom JR, Georgieff MK. Striking while the iron is hot: understanding the biological and neurodevelopmental effects of iron deficiency to optimize intervention in early childhood. *Curr Pediatr Rep*. 2014;2:291–298.
9. Berglund SK, Westrup B, Hägglöf B, et al. Effects of iron supplementation of LBW infants on cognition and behavior at 3 years. *Pediatrics*. 2013;131:47–55.
10. Ullrich C, Wu A, Armsby C, et al. Screening Healthy Infants for Iron Deficiency Using Reticulocyte Hemoglobin Content. *JAMA*. 2005;294(8):924–930. doi:10.1001/jama.294.8.924
11. Al-Ghananim RT, Nalbant D, Schmidt RL, et al. Reticulocyte hemoglobin content during the first month of life in critically Ill very low birth weight neonates differs from term infants, children, and adults. *J Clin Lab Anal*. 2016;30:326–334.
12. Parodi E, Giraudo MT, Davitto M, et al. Reticulocyte parameters: markers of early response to oral treatment in children with severe iron-deficiency anemia. *J Pediatr Hematol Oncol*. 2012;34:e249–e252.
13. Takala TI, Mäkelä E, Suominen P, et al. Blood cell and iron status analytes of preterm and full-term infants from 20 weeks onwards during the first year of life. *Clin Chem Lab Med*. 2010;48:1295–1301.
14. Ennis KM, Dahl LV, Rao RB, et al. Reticulocyte hemoglobin content as an early predictive biomarker of brain iron deficiency. *Pediatr Res*. 2018;84:765–769.
15. Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics*. 2010;126:1040–1050.
16. Buttrey SE. An excel add-in for statistical process control charts. *J Stat Softw*. 2009;30(13):1–12.

17. Institute for Healthcare Improvement. *The Breakthrough Series: Collaborative Model for Achieving Breakthrough Improvement*. IHI Innovation Series White Paper; 2003. http://www.ihi.org/resources/Pages/ IHIWhitePapers/The BreakthroughSeriesIHIs CollaborativeModelforAchie vingBreakthroughImp rovemen t.aspx. Accessed December 14, 2016.
18. Lorenz L, Peter A, Poets CF, et al. A review of cord blood concentrations of iron status parameters to define reference ranges for preterm infants. *Neonatology*. 2013;104:194–202.
19. Lorenz L, Peter A, Arand J, et al. Reference ranges of reticulocyte haemoglobin content in preterm and term infants: a retrospective analysis. *Neonatology*. 2017;111:189–194.
20. Lorenz L, Peter A, Arand J, et al. Reticulocyte haemoglobin content declines more markedly in preterm than in term infants in the first days after birth. *Neonatology*. 2017;112:246–250.
21. Parodi E, Giraudo MT, Ricceri F, et al. Absolute reticulocyte count and reticulocyte hemoglobin content as predictors of early response to exclusive oral iron in children with iron deficiency anemia. *Anemia*. 2016;2016:7345835.
22. Osta V, Caldirola MS, Fernandez M, et al. Utility of new mature erythrocyte and reticulocyte indices in screening for iron-deficiency anemia in a pediatric population. *Int J Lab Hematol*. 2013;35:400–405.
23. Banerjee J, Aladangady N. Biomarkers to decide red blood cell transfusion in newborn infants. *Transfusion*. 2014;54:2574–2582.
24. Nemeth E, Ganz T. The role of hepcidin in iron metabolism. *Acta Haematol*. 2009;122:78–86.
25. Collard KJ. Iron homeostasis in the neonate. *Pediatrics*. 2009;123:1208–1216.