Global Pediatric Health
Volume 4: 1–8

DOI: 10.1177/2333794X17703836
journals.sagepub.com/home/gph
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Iron Supplements for Infants at Risk for Iron Deficiency

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Abstract

Professional societies have published recommendations for iron dosing of preterm neonates, but differences exist between guidelines. To help develop standardized guidelines, we performed a 10-year analysis of iron dosing in groups at risk for iron deficiency: IDM (infants of diabetic mothers), SGA (small for gestational age), and VLBW premature neonates (very low birth weight, <1500 g). We analyzed iron dosing after red cell transfusions and erythropoiesis-stimulating agents (ESA). Of IDM, 11.8% received iron in the hospital; 9.8% of SGA and 27.1% of VLBW neonates received iron. Twenty percent of those who received iron had it started by day 14; 63% by 1 month. Supplemental iron was stopped after red cell transfusions in 73% of neonates receiving iron. An ESA was administered to 1677, of which 33% received iron within 3 days. This marked variation indicates that a consistent approach is needed, and using this report and a literature review, we standardized our iron-dosing guidelines.

Keywords

iron, iron deficiency, iron-deficient erythropoiesis, neurodevelopment

Received February 21, 2017. Accepted for publication March 8, 2017.

Introduction

Several professional societies have published recommendations for administering supplemental iron to neonates with risk factors for developing iron deficiency (Table 1).[1-6] Those guidelines primarily focus on premature neonates, but infants of diabetic mothers (IDM) and small-for-gestational-age neonates (SGA) are also at risk.[7-10] Disagreements occur regarding when iron dosing should begin, and what the daily iron dose should be. Moreover, variations exist regarding whether iron dosing should be stopped after a red blood cell (RBC) transfusion, and how iron is dosed accompanying erythropoiesis-stimulating agents (ESA; erythropoietin or darbepoetin). In general, when best practices have not been clearly established, implementing a consistent approach reduces variability and can lower costs and improve outcomes.[11-13]

Our recent pilot study suggested that about 17% of IDM, SGA, and VLBW premature neonates have biochemical iron deficiency at birth.[14] On that basis we speculated that some neonates could benefit from initiating iron well before the time recommended in any of the published guidelines.[1-6] As a step toward the consensus-building needed to develop a system-wide consistent approach to iron dosing in our neonatal intensive care units (NICUs), we analyzed 10 years of Intermountain Healthcare practice data.

Materials and Methods

This was a retrospective project involving neonates cared for in the 10-year period between January 2006

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Table 1. Recommendations for NICU Iron Supplementation.

	VLBW	SGA	IDM
Committee on Nutrition, American Academy of Pediatrics[1]	Start at 1 month. 2 mg/kg day if on human milk, 1 mg/kg/day if on formula	No specific recommendation	No specific recommendation
Nutrition Committee, Canadian Pediatric Society[2]	Start at 6 to 8 weeks. Birth weight ≥1000 g, 2-3 mg/kg/day. Birth weight <1000 g, 3-4 mg/kg/day.	No specific recommendation	No specific recommendation
Committee on Nutrition of the Preterm Infant, European Society of Paediatric Gastroenterology and Nutrition[3]	Start no later than 8 weeks. 2-2.5 mg/kg/day	No specific recommendation	No specific recommendation
American Academy of Nutrition and Dietetics[4]	Preterm infants; provide 2 mg/kg/day by iron-fortified formula or medicinal iron. Consider 4 mg/kg if at risk for iron deficiency or 5-6 mg/kg if iron deficient or on Epogen	No specific recommendation	No specific recommendation
World Review of Nutrition and Dietetics[5]	Start at 2 weeks. Birth weight <1500 g 2-3 mg/kg/day. Birth weight 1500-2000 g, 2 mg/kg/day; 6 mg/kg/day if on Epogen.	No specific recommendation	No specific recommendation
Centers for Disease Control and Prevention[6]	For breast-fed infants who were preterm or had a low birth weight, recommend 2-4 mg/kg per day of iron drops (to a maximum of 15 mg/day) starting at 1 month after birth and continuing until 12 months after birth.	No specific recommendation	No specific recommendation

Abbreviations: NICU, neonatal intensive care unit; VLBW, very low birth weight; SGA, small for gestation age; IDM, infants of diabetic mothers.

and December 2015 in the perinatal intensive care units of Intermountain Healthcare. Patients admitted to a NICU with a diagnosis of IDM, SGA, or VLBW were studied, because these have been reported as risk factors for developing iron deficiency.[8-10] IDM was defined as a neonate whose mother had the diagnosis of either pre-gestational diabetes mellitus (type 1 or type 2) or gestational diabetes (diagnosed during pregnancy). SGA was defined as a neonate with a birth weight <10th% lower reference interval of the Intermountain Healthcare normative data.[15] VLBW premature was defined as a neonate with a birth weight <1500 g and ≤34 weeks gestation. We determined whether each patient had any enteral or parenteral iron supplementation during their hospital stay, and if so when the dosing was begun.

Electronic pharmacy and NICU records were used from the following perinatal NICUs of Intermountain Healthcare: McKay-Dee Hospital Center, Ogden; LDS Hospital, Salt Lake City; Intermountain Medical Center, Murray; Utah Valley Regional Medical Center, Provo; and Dixie Regional Medical Center, St George. Intermountain Healthcare is a not-for-profit health care system operating 18 hospitals with labor and delivery units in Utah and Idaho. This quality report was approved for publication by the Intermountain Healthcare Institutional Review Board. Waiver from individual parental consent was granted because this was a de-identified, data-only quality report with appropriate privacy protection.

De-identified data were obtained from the Intermountain Healthcare Enterprise Data Warehouse by an authorized Intermountain Healthcare data analyst (Vickie L. Baer) and entered into and stored in a password-protected database. The program used for data collection into the Warehouse was a modified subsystem of clinical workstation. Clinical workstation is a web-based electronic medical record application that stores demographic and clinical information, such as history,

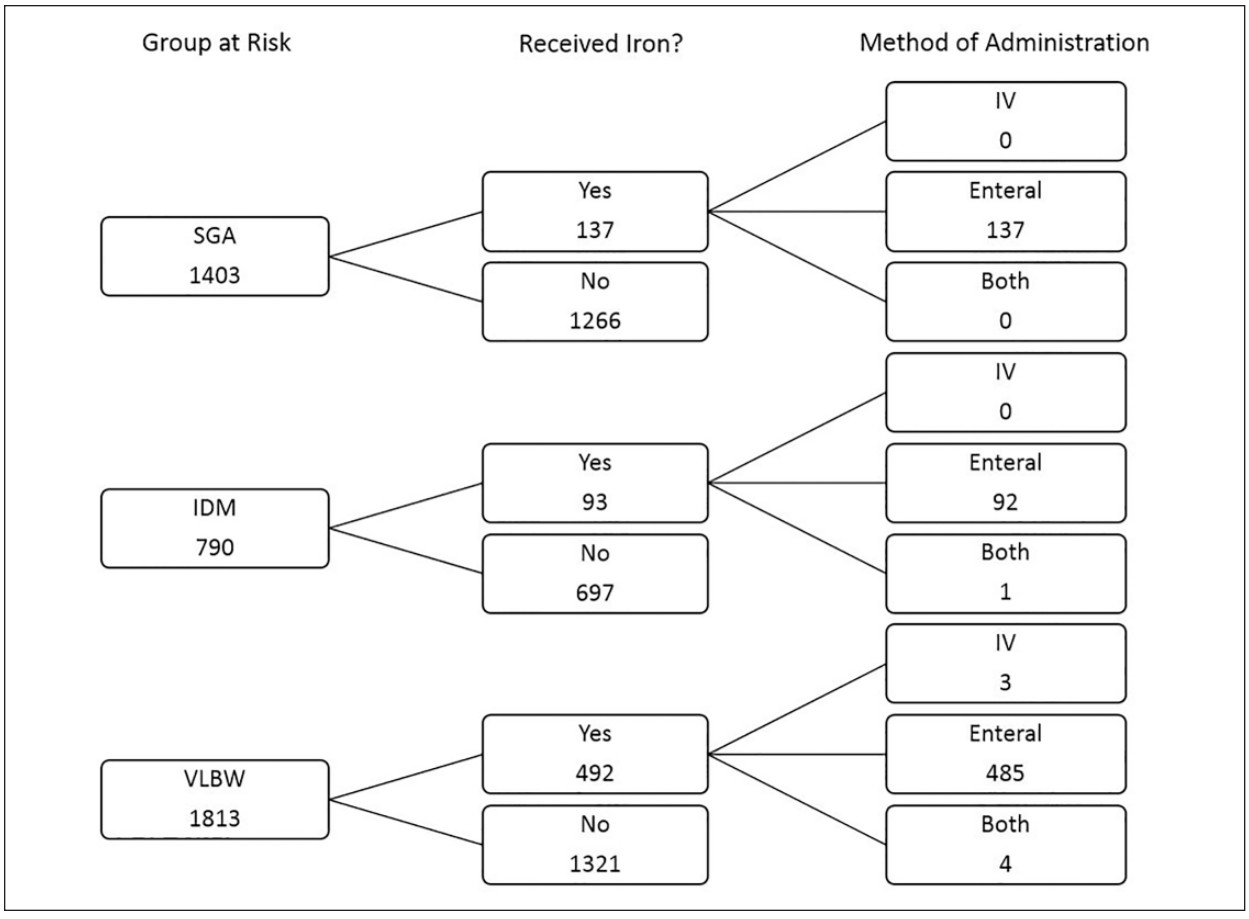

Figure 1. Supplemental iron dosing among 3 groups of neonates. Patients were included in this analysis if they were IDM, SGA, or VLBW and remained in an Intermountain Healthcare hospital for ≥14 days after birth, during the 10-year period (2006-2015).

physical examination results, laboratory data, problem lists, and discharge summaries. 3M Company (St Paul, MN) approved the structure and definitions of all data points within the program. Chi square with Yates correction (GraphPad Software, Inc, La Jolla, CA) was used to assess whether withholding iron after transfusion was different in the first 30 days after birth versus beyond 30 days. It was also used to assess whether giving iron after starting an ESA was different in the first 30 days after birth versus beyond 30 days. *P* values <.05 were considered to be significant.

Results

Figure 1 shows the number of patients in this analysis. Only neonates who remained in the hospital ≥14 days after birth were included, because none of the guidelines (Table 1) recommend commencing iron before 14 days. Of 790 IDM, only 11.8% received any supplemental iron in the hospital. Of 1403 SGA neonates, 9.8% received iron, and of 1813 VLBW preterm neonates, 27.1% received iron.

Figure 2 shows the day enteral iron was begun for the 722 IDM, SGA, and VLBW neonates who received any enteral iron dosing during their hospitalization. For all 3 groups, less than 20% of those who received supplemental iron had it started by day 14 (thus <20% were compliant with the World Review of Nutrition and Dietetics recommendations[5]), 55% to 60% had the iron started by day 30 (and thus were compliant with the American Academy of Pediatrics guidelines[1]), and 82% to 88% had it started by 8 weeks (56 days) (and thus were compliant with the European Society of Paediatric Gastroenterology and Nutrition guidelines[3]).

The percentage of IDM, SGA, and VLBW neonates who received enteral iron dosing in the NICU changed during the 10-year period studied, as shown in Figure 3. The trend was to give iron supplementation to lower percentages over this decade.

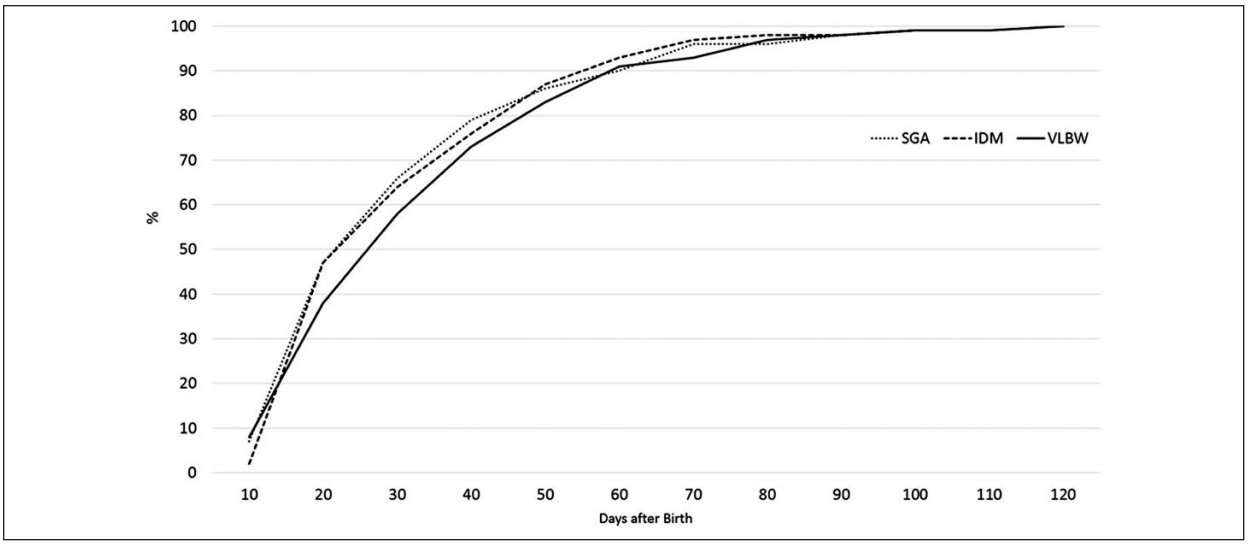

Figure 2. Analysis of when supplemental iron was begun (for those who received iron during their hospital stay). This analysis includes only IDM, SGA, and VLBW neonates who had enterally administered supplemental iron in an Intermountain Healthcare hospital from 2006 to 2015. The figure displays the cumulative percent of neonates in each of these 3 groups who had iron dosing.

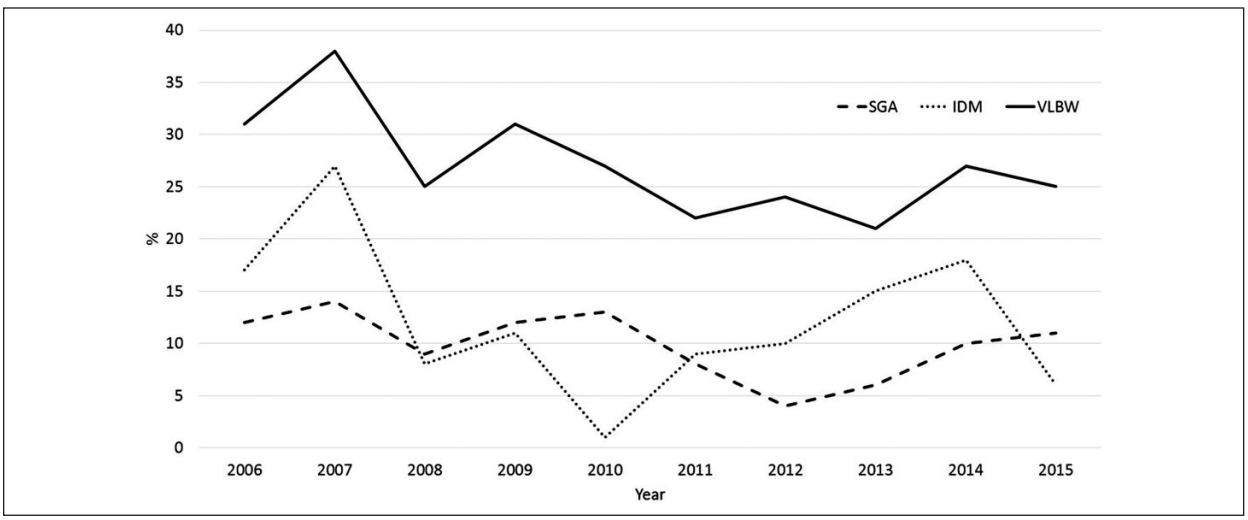

Figure 3. Supplemental iron administration over the 10-year period. This is an analysis of IDM, SGA, and VLBW neonates who remained in an Intermountain Healthcare hospital for at least 14 days after birth, during the period 2006 to 2015. The figure shows the yearly percentages of neonates who received supplemental iron during this 10-year period.

Stopping enteral iron dosing after an RBC transfusion was an inconsistent practice, as shown in Table 2. When supplemental iron was being administered on the day of a transfusion, iron dosing was stopped after 73% of transfusions. This was similar to whether the transfusion was given in the first 30 days (40 of 47 [85%] had iron dosing stopped) or after day 30 (53 of 76 [70%] had iron dosing stopped; $P = .38$). We were unable to find a pattern to explain this inconsistency other than individual physician preference. Inconsistency was present within each NICU over the 10 years reviewed.

The practice of ordering iron supplementation when ESAs were administered was also inconsistent, as shown in Table 3. This was the case whether the ESA was given during the first 30 days or beyond 30 days following birth ($P = .09$). Inconsistency was present within each NICU over the 10 years reviewed.

Table 2. Iron Supplementation Following RBC Transfusion[a].

	RBC Transfusion Between Birth and Day 14 (N = 4)	RBC Transfusion Between Day 15 and Day 30 (N = 47)	RBC Transfusion After Day 30 (N = 76)
Iron dosing continued after transfusion	0	11 (33%)	23 (30%)
Iron dosing suspended after transfusion	4 (100%)	36 (67%)	53 (70%)

Abbreviation: RBC, red blood cell.
[a]When supplemental iron was being administered before the transfusion, was it continued or was it stopped after the transfusion?

Table 3. Iron Supplementation Accompanying Administration of an Erythropoiesis-Stimulating Agent (ESA) (Erythropoietin or Darbepoetin) to IDM, SGA, and VLBW Premature Neonates[a].

	ESA Was Given Between Birth and Day 14 (N = 551)	ESA Was Given Between Day 15 and Day 30 (N = 527)	ESA Was Given After Day 30 (N = 599)
Iron given IV	2 (0.4%)	2 (0.4%)	2 (0.3%)
Iron given enterally	163 (29.6%)	206 (39.1%)	180 (30.1%)
Iron not given	386 (70.0%)	319 (60.5%)	417 (69.6%)

Abbreviations: IDM, infants of diabetic mothers; SGA, small for gestation age; VLBW, very low birth weight; IV, intravenous.
[a]Shown are cases where an ESA was given and iron was administered at the time of, or up to within 3 days after, the ESA dose. Values are shown as absolute number and percent.

Discussion

Iron supplementation is a common NICU practice, and it should have a scientific evidence base. However, an evidence base is currently lacking, leading to inconsistent neonatal iron dosing recommendations by various professional societies. As examples, the World Review of Nutrition and Dietetics suggests initiating iron supplementation for preterm infants at 2 weeks of age,[5] the American Academy of Pediatrics at 1 month,[1] the Canadian Pediatric Society at 6 to 8 weeks,[2] and the European Society of Paediatric Gastroenterology and Nutrition at no later than 8 weeks.[3]

Iron deficiency at critical periods of early postnatal brain development can have adverse neurodevelopmental consequences.[16,17] However, too much enteral iron can have adverse effects as well, including emesis, diarrhea or constipation, or other abdominal distresses.[18] Also, free iron in the blood, not bound to transport proteins such as transferrin or lactoferrin, can be a potent oxidizing agent, potentially adding to oxidant damage of the lungs and retinas of preterm neonates.[19]

It is a worthwhile goal to develop a personalized medicine practice, where each NICU patient receives iron supplementation at a time, dose, and preparation that is ideal for the needs of that individual. The relationship between early iron deficiency and permanent neurodevelopmental delays makes this goal particularly compelling.[3,16,17] However, at the present time it is unclear how we should identify the unique iron needs of each NICU patient. For instance, the tests used to assess individual iron needs require better definition, and means of serial monitoring with noninvasive and reliable methods must be developed. Using a consistent approach to iron dosing for NICU patients at risk for iron deficiency is superior to the present inconsistent situation that can cause frustrating variations, increased costs, and worse outcomes.[11-13]

As a step toward developing evidence-based iron dosing practices at Intermountain Healthcare, we analyzed 10 years of practice data from our multi-NICU system. We studied IDM, SGA, and VLBW neonates because these groups have been reported to be at risk for developing iron deficiency.[8-10] We focused on the day iron supplements were initiated, and the practices related to iron dosing after RBC transfusions and accompanying ESA administration. We found considerable variation in each aspect.

In developing guidelines acceptable to each of our NICUs, we were influenced by our recent finding of biochemical iron deficiency in 17% of the IDM, SGA, and VLBW neonates we screened at birth.[14] We are currently engaged in a much larger validating study to identify NICU patients with iron deficiency and to assess the pathogenesis. Meanwhile, for iron guideline development, we elected to adopt a modification of the recommendation of the World Review of Nutrition and Dietetics, which advocates starting iron supplementation at 2 weeks.[5] Our new guideline is to initiate enteral

iron dosing for IDM, SGA, and VLBW neonates at 10 to 14 days if they are feeding >100 mL/kg/day, and to use intravenous dosing for any who are not feeding this amount by 14 days (see Supplemental Material, available online at http://journals.sagepub.com/home/gph). In this way, the IDM, SGA, and VLBW neonates in our NICU system should have iron supplements begun at or before the time recommended in one of the more aggressive international iron dosing guidelines.[5]

Some Intermountain Healthcare neonatologists advocate withholding iron supplements for 2 weeks following each RBC transfusion to avoid iron overload from the iron in the donor red cells plus the enteral iron. Indeed, an elevation in serum ferritin can occur in neonates after multiple NICU transfusions.[20] However, transfusion-acquired iron overload occurs primarily in neonates with hemolytic disorders,[21] where iron from repeated transfusions is not eliminated and can substantially increase the total body iron content. In contrast, iron overload is not a common problem among neonates transfused on the basis of phlebotomy losses or external hemorrhage, because the transfused blood basically replaces the iron lost, and thus does not create an increasing body iron burden. In our present study, we found that enteral iron supplements were stopped after 73% of NICU transfusions. In formulating our new guidelines, we judged it reasonable to withhold supplemental iron after RBC transfusions in neonates with hemolytic disorders, but not after transfusions given for the anemia of phlebotomy losses or external hemorrhage (see Supplemental Material, available online at http://journals.sagepub.com/home/gph).

Iron supplementation can be given enterally or intravenously and various preparations are available for each. CosmoFer (intravenous iron dextran) is a low-molecular-weight iron dextran that has been given to preterm neonates described in case reports and studies, with no adverse effects identified, and is Food and Drug Administration (FDA) approved in infants 4 months and older.[22-25] However, iron dextran has an FDA black box warning due to its association with anaphylactic reactions. Intravenous iron sucrose (Venofer, Vifor International), may have safety advantages[25] and is the current intravenous iron preparation we use in the Primary Children's Hospital Hematology clinic (Yaish and colleagues, 2017, unpublished data). Iron sucrose is FDA approved in children ≥2 years of age.[25]

Meta analyses and reviews suggest that iron supplements should be given to neonates treated with an ESA (erythropoietin or darbepoetin).[26,27] We found that within 3 days after initiating ESA treatment only about one third of IDM, SGA, or VLBW neonates had supplemental iron ordered. ESAs will be less effective if iron deficiency develops. Moreover, aggravating iron deficiency by administering ESAs to neonates who already have biochemical iron deficiency[14] could divert iron required for brain development into erythropoiesis.[28]

We recognize limitations of our study. First, our databases contain only in-patient information; thus, we cannot track iron dosing after hospital discharge. Although iron dosing can, and probably in many cases should, begin during the NICU stay, much of the iron dosing is in the outpatient setting. Second, our databases are limited regarding iron intake from iron-fortified formulas and human milk fortifiers; thus, what we report as enteral iron intake is a minimal estimate, including only the iron given as a medication. Third, our records were not sufficient to determine the exact doses of supplemental iron our neonates received, daily or in total. Fourth, the only enteral iron preparation we administered during this period was ferrous sulfate, but other preparations might have advantages. Similarly, the only intravenous iron preparation we administered during this period was iron dextran, but other preparations such as iron sucrose almost certainly have advantages.[25] Finally, we have no information regarding the adequacy of the iron we administered during this 10-year period to prevent iron deficiency, nor do we know whether any patients received iron in excess of their iron requirements or developed problems therefrom. Such information is essential to developing best-practice iron dosing, but this must await studies that randomize neonates to various iron treatment groups and report short-term as well as intermediate and long-term neurodevelopmental outcomes.

Until definitive studies have been conducted and reported, and until we can engage in a personalized medicine approach for iron dosing of each individual NICU patient, we maintain that adopting a consistent approach to iron dosing is better than continuing with our widely divergent dosing practices.[11-13] The Online Supplemental Material (available online at http://journals.sagepub.com/home/gph) contains the guidelines we agreed to use in the Intermountain Healthcare NICUs until evidence-based and personalized iron dosing is available from our own ongoing studies and/or from the studies of others.

Author Contributions

BCM: Contributed to conception and design; contributed to acquisition; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

VLB: Contributed to acquisition and analysis; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

DMS: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

CYL: Contributed to conception and design; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

EAO: Contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

CB: Contributed to conception; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

EH: Contributed to design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

REF: Contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

RDC: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Supplemental material

The online supplementary material is available at http://journals.sagepub.com/doi/suppl/10.1177/2333794X17703836.

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