Supplemental Iron and Recombinant Erythropoietin for Anemia in Infants Born Very Preterm: A Survey of Clinical Practice in Europe

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Objectives To survey practices of iron and recombinant human erythropoietin (rhEpo) administration to infants born preterm across Europe.

Study design Over a 3-month period, we conducted an online survey in 597 neonatal intensive care units (NICUs) of 18 European countries treating infants born with a gestational age of <32 weeks.

Results We included 343 NICUs (response rate 56.3%) in the survey. Almost all NICUs (97.7%) routinely supplement enteral iron, and 74.3% of respondents to all infants born <32 weeks of gestation. We found that 65.3% of NICUs routinely evaluate erythropoiesis and iron parameters beyond day 28 after birth. Most NICUs initiate iron supplementation at postnatal age of 2 weeks and stop after 6 months (34.3%) or 12 months (34.3%). Routine use of rhEpo was reported in 22.2% of NICUs, and in individual cases in 6.9%. RhEpo was mostly administered subcutaneously (70.1%) and most frequently at a dose of 250 U/kg 3 times a week (44.3%), but the dose varied greatly between centers.

Conclusions This survey highlights wide heterogeneity in evaluating erythropoietic activity and iron deficiency in infants born preterm. Variation in iron supplementation during infancy likely reflects an inadequate evidence base. Current evidence on the efficacy and safety profile of rhEpo is only poorly translated into clinical practice. This survey demonstrates a need for standards to optimize patient blood management in anemia of prematurity. *(J Pediatr 2025;276:114302)*.

A physiological decline in hemoglobin concentration occurs in all neonates during the first weeks after birth. In infants born very preterm, this process, termed anemia of prematurity (AOP), is exacerbated initially by iatrogenic phlebotomy losses.[1,2] AOP is characterized by iron deficiency, low endogenous erythropoietin (Epo) plasma concentrations, and a shorter lifespan of red blood cells (RBC; 40-60 days vs 120 days in adults).[1] Thus, routine patient blood management of infants born preterm, defined as a multimodal, multidisciplinary patient-centered strategy aimed at minimizing the use of blood products and improving patients' outcomes, deserves clinical attention in the course of postnatal care. One treatment option for anemia is RBC transfusion,

AOP	Anemia of prematurity
Epo	Erythropoietin
ESAs	Erythropoiesis-stimulating agents
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology, and Nutrition
NICUs	Neonatal intensive care units
RBCs	Red blood cells
RCTs	Randomized controlled trials
Ret-HE	Reticulocyte hemoglobin
rhEpo	Recombinant human erythropoietin
ROP	Retinopathy of prematurity

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but there are associated risks with using this adult donor-derived blood component and optimal transfusion thresholds have not yet been fully defined for all subgroups of infants.[3] Other prevention and treatment options for supporting endogenous hematopoiesis include supplementation of iron and administration of recombinant human Epo (rhEpo).[4]

There is a long history of iron supplementation in the care of infants born preterm. Iron hemostasis is impacted by prematurity because iron is mostly actively transferred from the mother to the fetus in the third trimester of pregnancy.[5] Assessment of the iron status in preterm neonates is challenging, owing to lack of gestational and postnatal age-specific normal reference values. In addition, there is variability in the diagnostic value of laboratory parameters in systemic pathologic conditions, like hypoxia or inflammation.[6,7] Besides its key role in erythropoiesis, iron also has important functions in the central nervous system, contributing to brain growth, myelination, and neurotransmitter and energy production.[8] Thus, iron deficiency in early childhood is a risk factor for impaired neurodevelopment.[9] The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) provides a guideline for prophylactic enteral iron supplementation to avoid iron deficiency in infants born preterm.[10]

International recommendations for the use of erythropoiesis-stimulating agents (ESAs), such as rhEpo and darbepoetin, are lacking, but several randomized controlled trials (RCTs) have been conducted in the population of infants born preterm. These vary significantly concerning timing, dosing, application (intravenously or subcutaneously), and duration of rhEpo treatment.[4,11,12] The Cochrane meta-analysis on early postnatal use of rhEpo (2006) and its updates (2012, 2014) reported an increased risk of retinopathy of prematurity (ROP).[13-15] However, more recent updates of the Cochrane review and additional studies did not find an association between early rhEpo and ROP.[4,16]

Given the uncertainties regarding optimal use of iron, rhEpo and other nontransfusion alternatives for managing AOP, we conducted this survey to describe current practices of iron supplementation and rhEpo in European neonatal intensive care units (NICUs).

Methods

This survey was performed by the Neonatal Transfusion Network (www.neonataltransfusionnetwork.com), an international research group that aims to improve clinical practice in neonatal transfusion medicine. Methods for designing and distributing the survey were recently published.[17] This survey contained 3 questions on iron use, addressing indication, initiation and cessation of treatment, 4 questions on rhEpo use, addressing indication, initiation, administration route, dose and modification of the given dose, and 1 question on routine blood testing at 28 days of age for investigating erythropoietic activity and iron parameters in anemic infants (**Appendix 1**, online; available at www.jpeds.com). In both iron and rhEpo sections, multiple answers were possible. These questions were entered into LimeSurvey (Hamburg, Germany). Neonatologists from 18 European countries, who served as national coordinators, disseminated the questionnaire between October and December 2020 to 597 NICUs providing care for infants born at <32 weeks of gestation. A single response per NICU was requested. Ethical approval was not required because no patient-specific data were collected.

The LimeSurvey data were extracted into Statistical Package for the Social Sciences (IBM, SPSS 27.0, IBM, Armonk, NY) for data cleaning and analysis, which was performed by 2 authors working independently. Confirmed double entries, ineligible responses, and responses that were >75% blank were excluded. In addition, after reviewing the responses concerning rhEpo, a post hoc classification was made into routine rhEpo administration (centers that answered yes to the question asking whether they routinely use rhEpo and who selected a corresponding indication) and individualized administration (centers, that answered no to the question asking whether they routinely use rhEpo, but provided a comment on exceptional cases in which rhEpo is given and also answered ≥2 of the 3 other questions on initiation, route of administration, and dose). Two sensitivity analyses included in our previous publication on transfusion practice suggested that significant bias owing to response rate variations between countries as well as nonresponse bias are unlikely.[17]

Results

From the 343 responses included in this survey,[17] we excluded 9 responses on rhEpo owing to inconsistent answers, resulting in a response rate on rhEpo of 55.9% (334/597). Inconsistent responses included (a) centers that either stated not routinely using rhEpo, but subsequently provided either dose or route of application, but without specifying the indication, and (b) centers that answered yes on routine use rhEpo, but without specifying the indication, dose or route of administration.

We included the following number of NICUs: Austria (7/7 NICUs concerning the answers on iron; 7/7 NICUs concerning the questions on rhEpo), Belgium (16/19; 16/19), Finland (5/5; 5/5), Germany (112/160; 111/160), Hungary (21/21; 20/21), Italy (49/105; 47/105), Malta (1/1; 1/1), the Netherlands (9/9; 9/9), Norway (6/6; 6/6), Poland (18/36; 16/36), Portugal (10/11; 10/11), Romania (4/19; 4/19), Slovakia (10/13; 8/13), Slovenia (3/4; 3/4), Spain (41/111; 41/111), Sweden (8/8; 7/8), Switzerland (6/8; 6/8), and the UK (17/55; 17/55).[17]

Strategies for Detecting or Evaluating AOP

Nearly two-thirds, 65.3% (224/343), of NICUs reported routine blood testing to investigate anemia in infants at 28 days of age. Of these, 60.7% (136/224) evaluated

reticulocyte counts and/or another parameter reflecting iron storage or metabolism on day 28 (Table I). In German-speaking countries (Austria, Germany, and Switzerland), where many centers participated in the Effects of Liberal vs Restrictive Transfusion Threshold on Survival and Neurocognitive Outcomes in Extremely Low Birth-Weight infants (ETTNO) trial,[18] a higher percentage of NICUs abstained from routine blood examinations (40% vs 27% in all other countries). Notably, the most common measure of iron storage or metabolism used by centers undertaking blood testing was ferritin levels (80/224 [35.7%]), followed by serum iron concentrations (49/224 [21.9%]), reticulocyte hemoglobin (Ret-HE) content (13/224 [5.8%]) and transferrin saturation (12/224 [5.4%]) or concentration (9/224 [4.0%]) (Table I).

Iron Supplementation

Of the 343 NICUs, 335 (97.7%) routinely supplement iron. Nearly three-quarters reported a gestational age at birth <32 weeks as an indication, followed by a birth weight od <1500 g (Table II). Timing of initiation varied mainly between 2 (48.7%) and 4 (20.0%) weeks after birth, with some centers starting at <2 weeks (1.8%) or >4 weeks of age (0.6%). Almost one-third (29.7%) of NICUs start iron treatment when infants were on complete enteral nutrition (Table II). Most NICUs stop iron supplementation after 6 or 12 months (34.3% each) (Table II).

rhEpo

Of 334 responses on rhEpo, 237 (70.9%) reported never using rhEpo. Among the 97 centers treating anemia with rhEpo, 74 reported routine use (74/334 [22.2%]), and 23 used rhEpo based on individualized decision (23/334 [6.9%]). The response rate to the question of whether rhEpo was used did not differ between academic and nonacademic centers. Of the 97 centers that reported administering rhEpo (routinely or individually), 46 (47.4%) were academic centers and 51 (52.6%) were nonacademic centers. Of the 46 academic centers, 36 reported routine use (36/46 [78.3%]) and 10 centers (10/46 [21.7%]) reported individual use. Among the nonacademic centers, 38 centers (38/51 [74.5%]) routinely administered rhEpo and 13 (13/51 [25.5%]) used it on an individual basis. In an additional subgroup analysis of centers participating in the ETTNO trial, the ratio between centers never using rhEpo (75.9%) vs centers routinely using rhEpo (24.1%) was similar to when compared with non-ETTNO centers. However, concerning the ETTNO centers, routine use was only reported from academic centers (Appendix 2, online; available at www.jpeds.com). Where rhEpo was used routinely, gestational age at birth of <32 weeks was the predominant indication for rhEpo (52/97 [53.6%]), followed by considered high risk for ROP (25/97 [25.5%]) (Table III). Approximately one-quarter of the responders (23/97) started rhEpo treatment within the first week of life, whereas 29% of units (28/97) initiate treatment after day 7. The remaining NICUs used other starting criteria. A dosage of 250 IU/kg 3 times per week was reported by 44.3% (43/97) of NICUs, but other dosages were also reported (3 × 300 IU/kg per week or 3 × 400 IU/kg per week) (Table III). There was no significant difference in rhEpo dosing in infants with early (before day 8) or late (on day 8 or later) initiation of treatment (Figure). In most NICUs (68/97 [70.1%]),

Table I. Investigations routinely performed at 28 days of age for AOP in preterm infants born <32 weeks gestational age

Routine blood testing	224/343 (65.3)
Reticulocyte count	136 (60.7)
Serum iron concentration	49 (21.9)
Ferritin concentration	80 (35.7)
Others	52 (23.2)
Top 4 free-text answers	
Ret-He content	13 (5.8)
Transferrin saturation	12 (5.4)
Transferrin concentration	9 (4.0)
Hemoglobin/Hematocrit	6 (2.7)

Values are number (%).
Double entries possible, n = 82 centers with double entries, of which n = 11 with triple entries.

Table II. Current practice on iron supplementation in preterm infants born <32 weeks gestational age in 335 NICUs

Numbers and percentages of NICUs	No.	%
Routine iron supplementation, if		
Gestational age at birth <32 weeks	249	74.3
Gestational age at birth <28 weeks	75	22.4
BW <1500 g	153	45.7
BW <1000 g	68	20.3
Others (top 4 free-text answers)	64	19.1
BW <2500 g	17	5.1
BW <2000 g	9	2.7
Gestational age <35 weeks	8	2.4
Gestational age <34 weeks	6	1.8
Initiation of iron supplementation, if		
2 weeks after birth	163	48.7
4 weeks after birth	67	20.0
Partially enterally fed	70	20.9
Totally enterally fed	98	29.3
Others (top 5 free-text answers)	46	13.7
<2 weeks after birth	6	1.8
3 weeks after birth if enteral feeding >100 mL/kg/d	13	3.9
If enteral feeding >100 ml/kg/d	5	1.5
If rhEPO treatment is initiated	3	0.6
Depending on ferritin or ferritin saturation	4	1.2
Stop of iron supplementation		
After 3 months	31	9.2
After 6 months	115	34.3
After 12 months	115	34.3
Neonatologist not responsible	60	17.9
Not known by the neonatologist	6	1.8
Others (top 3 free-text answers)	60	17.9
When weaned from milk	23	6.7
Decision by pediatrician	5	1.5
Depends on Hct/Hb or ferritin	4	1.2

BW, birth weight.
Double entries possible, n = 160 centers with multiple answers for indication of iron supplementation, n = 108 with multiple answers for initiation of iron supplementation and n = 44 with multiple answers for stop of iron supplementation.

Table III. Current practice on rhEpo treatment in preterm infants born <32 weeks gestational age

NICUs never using rhEpo, number (percentage)	237/334 (70.9%)	
NICUs using rhEpo, number (percentage)	97/334 (29.1%)	
	No.	%
Routine rhEpo treatment	74/334	22.2
Individualized decision on the use of rhEpo	23/334	6.9
Time of initiation		
Straight after birth	5	5.2
Within the first 7 days after birth	23	23.7
After day 7	28	28.9
Other (top 2 free-text answers)	38	39.2
When on iron supplementation	6	6.2
In case of anemia/depends on hemoglobin/hematocrit	6	6.2
Indication for treatment with rhEpo		
Gestational age at birth <32 weeks	52	53.6
BW <1000 g	6	6.2
BW <1500 g	5	5.2
Considered high risk for necrotizing enterocolitis	9	9.3
Considered high risk for ROP	8	8.2
Other (top 2 free-text answers)	25	25.5
Lack of consent for RBC transfusion	3	3.1
Jehovah's Witnesses	5	5.2
Dosing of rhEpo		
250 IU/kg 3× per week	43	44.3
300 IU/kg 3× per week	4	4.1
400 IU/kg 3× per week	7	7.2
Other	34	32.0
Route of rhEpo administration		
Intravenously	11	11.3
Subcutaneously	68	70.1
Intravenously first, subcutaneously later	27	27.8

BW, birth weight.
Nine centers were excluded owing to inconsistent responses. Double entries possible for indication, dose and route of rhEpo administration. Twelve centers with multiple answers for indication of rhEpo, 2 centers with double entries for dose of rhEpo administration and 9 centers with multiple selections for route of rhEpo administration. Three answers missing for initiation of rhEpo treatment, 10 answers missing for indication of treatment, 2 answers missing for route, and 11 answers missing for dose of rhEpo treatment.

rhEpo is administered subcutaneously; 27 units (27.8%) responded that they give rhEpo intravenously first and then change to subcutaneous injection when intravenous access is no longer available. The routine use of rhEpo within the individual countries varied from 0% to 100%, with highest frequency in Slovenia (3/3), Austria (4/7), Spain (16/41), Poland (5/16), Italy (12/47), and Germany (27/111) (Table IV).

Discussion

Our findings identify marked heterogeneity in current practice of iron supplementation and rhEpo treatment in infants born preterm, as well as in evaluating erythropoietic activity. Iron is administered routinely in infants born very preterm, with differences mainly in duration of treatment. RhEpo is routinely used in one-fifth of NICUs, but the indication, as well as initiation and dose, vary widely across Europe. More generally, this survey broadens our knowledge on current practice toward a limited evidence base for patient blood management in infants born very preterm. Although the implication of diagnostic blood loss during intensive care of infants born very preterm (especially within the first 7 days) is well-known,[19] 2 of 3 NICUs routinely perform blood examinations that include cellular and nonhematological parameters reflecting erythropoietic activity or iron metabolism in infants born preterm at around day 28 after birth. The rationale for this analysis remains unclear, especially because many of the currently used laboratory parameters do not provide sufficient analytic and predictive value to adequately evaluate endogenous erythropoietic activity. A quantitative reticulocyte analysis is widely measured. Although it is generally assumed that a high relative or absolute reticulocyte count indicates appropriate endogenous erythropoietic activity, a low or normal reticulocyte count may be difficult to interpret, if erythropoiesis is not suppressed by a previous RBC transfusion.[20,21] Ret-He as a relatively novel marker, indicating sufficient iron incorporation into newly produced progenitor cells,[22] might be routinely accessible only to a limited number of European NICUs. This finding is in contrast with current practice in the US, where a recent survey indicates that Ret-He is the most popular biomarker for monitoring iron sufficiency.[23] Although ferritin is less commonly used in the US to monitor iron sufficiency,[23] it is still the most common surrogate parameter for iron deficiency chosen by European NICUs. However, ferritin acts as acute phase response protein and has only limited value as a marker of iron sufficiency in infants born preterm.[24] Ret-He is better correlated with the classical measure of MCV as a marker of iron-limited erythropoiesis than ferritin. Furthermore, no additional blood sample is required for its analysis.[25] Although other, noncellular parameters (serum iron or transferrin concentration, transferrin saturation) are also not superior to Ret-He,[26] hepcidin, the main regulator of iron hemostasis, may be a useful measure in infants born preterm treated with rhEpo.[27] Thus, patient blood management strategies in preterm neonates should be supported by the development of a consistent approach for the assessment of anemia, which might include measures of cardiac or circulatory distress (by echocardiography) and blood oxygenation capacity, as suggested by the association of low pretransfusion cerebral oxygenation with unfavorable outcomes in the Transfusion of Prematures (TOP) trial.[28]

Our survey indicates that, in Europe, almost all infants born preterm with a gestational age of <32 weeks receive iron supplementation, a similar finding as reported in the US (94.7%).[23] In Europe, iron supplementation was mostly (68.7%) initiated within the first 2-4 weeks after birth, corresponding to the ESPGHAN guideline, which recommends prophylactic enteral iron supplementation from 2 to 6 weeks of age (2-4 weeks in extremely low birth weight infants).[10] The World Health Organization and the American Academy of Pediatrics recommend iron supplementation starting by 1 month of age to prevent oxidative stress caused by non-transferrin-bound iron overload.[29,30] This survey also indicates that—as in the US—the infants' enteral feeding status influences when iron supplementation is started, with

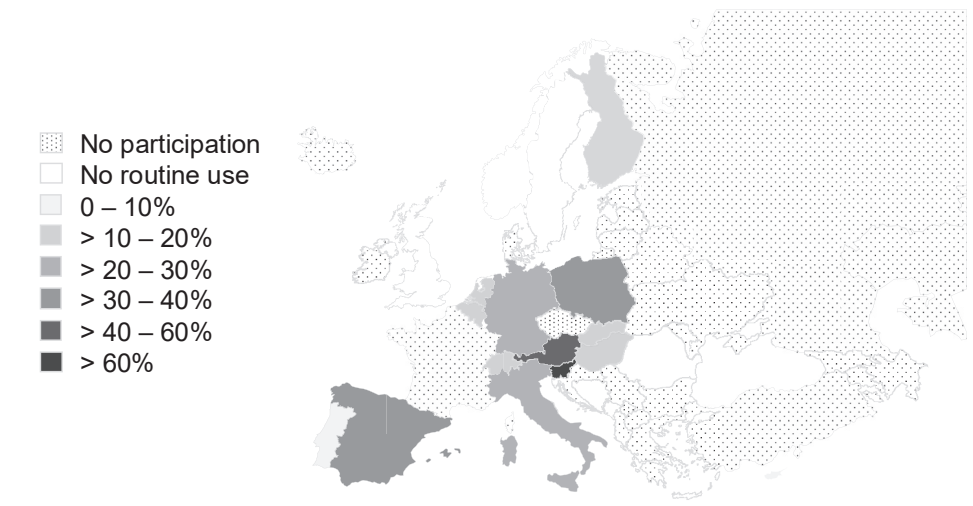

Figure. Map on the use of rhEpo in preterm infants born <32 weeks gestational age in European NICUs. The intensity of grey scales indicates the frequencies per country.

equal numbers of European NICUs initiating in partially vs totally enterally fed infants. This variability may be related to the current ESPGHAN guideline, which does not provide a recommendation on the minimal volume of enteral nutrition when iron supplementation is initiated.[10]

The duration of iron supplementation is also characterized by significant variability in length of treatment (6 vs 12 months). Although the ESPGHAN guideline recommends that iron supplementation should be continued after discharge, at least until 6-12 months of age depending on diet (without further specification),[10] the American Academy of Pediatrics guideline recommends extension through 12 months of age.[29] A recent systematic review indicates significant lack of data on the duration of iron supplementation,[31] although a recent retrospective cohort study in infants born very preterm who received prophylactic iron supplements starting at 2-4 weeks after birth showed a high prevalence of iron deficiency (~32%) as evaluated by serum ferritin concentrations at 4 or 6 months corrected age.[32] We also found significant differences in responsibility for decision-making (neonatologist, midwife, or pediatrician).

Table IV. Distribution of rhEpo administration per country

Country	Routine use, No. (%)	Individual use	Valid answers
Slovenia	3 (100)	0	3/3
Austria	4 (57)	1 (14)	7/7
Spain	16 (39)	2 (5)	41/41
Poland	5 (31)	2 (13)	16/18
Italy	12 (26)	4 (9)	47/49
Germany	27 (24)	3 (3)	111/113
Finland	1 (20)	1 (20)	5/5
Switzerland	1 (16)	0	6/6
Hungary	3 (15)	2 (10)	20/21
Slovakia	1 (12)	2 (25)	8/10
Portugal	1 (10)	2 (20)	10/10
Belgium	0	2 (12)	16/16
The Netherlands	0	1 (11)	9/9
UK	0	1 (6)	17/17
Malta	0	0	1/1
Norway	0	0	6/6
Romania	0	0	4/4
Sweden	0	0	7/8
Overall	74	23	334

The percentage of centers using rhEpo within a country is shown in parentheses.

Our survey indicates a low frequency of use of ESAs in European NICUs, although the most recent Cochrane meta-analysis and PENUT confirmed that early administration of ESAs reduces the number and volume of RBC transfusions, and donor exposure.[4,33] A similar observation (~39%) has been previously made in a survey that included 142 NICUs from Germany (79 NICUs) and other European countries (63 NICUs),[34] and in an international survey (routine use of rhEpo in ~26%) that included 5 European countries.[35] Most recently, the aforementioned survey in the US including 56 level III NICUs also reported the use of rhEpo or ESA in 34% of centers.[23] Taken together, this finding suggests that, currently in Europe 71% and in the US, 66% of NICUs never use rhEpo or ESA. It has been speculated that the restrictive use of rhEpo resulted from safety concerns based on a previous Cochrane meta-analysis on the early use of rhEpo (2006-2014), reporting an increased risk of higher stage ROP (ROP ≥3).[13-15] As a result, the European Medicines Agency and subsequently national authorities (eg, in Germany) as well as the US Food and Drug Administration warned that an additional risk of ROP associated with rhEpo treatment in infants born very preterm could not be excluded.[36,37] However, recent

updates of this Cochrane review and additional studies did not find an association between early rhEpo and ROP.[4,16]

In contrast with the previous European survey,[34] the number of NICUs initiating rhEpo treatment straight after birth, likely intended for neuroprotection in infants born very preterm,[38,39] was much lower (5.2% vs 27.0%). This difference likely reflects the results of 2 large RCTs that could not confirm a significant benefit of early high-dose rhEpo on neurodevelopmental outcome at 20-24 months of age or on behavior and quality of life at 5 years of age, which were published in 2020-2022.[12,40,41] If compared with the previous European survey and a retrospective multicenter cohort analysis in the US,[34,42] the current survey suggests a trend toward an earlier or more individualized initiation of rhEpo treatment, possibly reflecting the discussion on the arbitrary definition of early vs late rhEpo in the meta-analyses of Cochrane Library.[43] The finding that in Europe almost 20% of NICUs routinely or occasionally use rhEpo for the prevention of ROP and necrotizing enterocolitis is novel. This may result from the publication of a recent meta-analysis on secondary outcome measures in infants born preterm who received rhEpo for neuroprotection, which showed a lower incidence of necrotizing enterocolitis and ROP in rhEpo treated infants.[44] It may also reflect the understanding that a higher incidence of ROP and necrotizing enterocolitis has been associated with severe anemia or earlier and more intense RBC transfusions.[45-48] Indeed, the post hoc analysis of the Preterm Erythropoietin Neuroprotection Trial (PENUT) trial indicates that the risk of transfusion number, volume, and donor exposures can be significantly decreased in infants with gestational age <28 weeks or with birth weight of <1000 g, when treated with rhEpo.[12,33] We also observed a trend toward higher rhEpo dosing and preferred subcutaneous administration when compared with the previous survey (70% vs 49%).[34] This change in practice may reflect the findings of the PENUT trial. In comparison with RCTs performed between 1990 and 2010 on rhEpo to treat or prevent AOP,[11] the participants in the PENUT trial received somewhat higher doses, starting after birth with rhEpo 1000 IU/kg intravenously every 48 hours for 6 doses, followed by maintenance dosing of 400 U/kg per dose by subcutaneous injection 3 times a week until 32 weeks gestational age.[12] The rationale for subcutaneous instead of intravenous application is supported not only by the aim to decrease patients' days with peripheral or central lines, but also to prevent urinary loss of rhEpo after intravenous vs subcutaneous application.[49]

This survey has also some general limitations common to all surveys. The survey did not attempt to elucidate the volumes of diagnostic blood loss by routine withdrawals and their relevance on blood transfusion requirement. Any data on iron dosing were not obtained in this survey. Although likely relevant, the adaptation of iron supplementation in the context of rhEpo treatment has also not been considered.[50] Strengths of this survey include the relatively high response rate despite the ongoing pandemic and the wide range of countries included.[17] Given the recent publications on potential benefits of rhEpo treatment,[4,33,46] and on the diagnostics of iron metabolism (eg, by measuring hepcidin concentrations),[27] this survey is timely, provides a valuable starting point for further studies, and highlights the need for guideline development.

Despite available guidelines and a degree of concordance on administration strategies for iron supplementation, our survey indicates many areas of variable practice. The burden of anemia may be higher after recent RCTs advocating for more restrictive hemoglobin thresholds for RBC transfusion, which adds importance to understand the clinical impact of iron status on anemia and long-term clinical outcomes. One area of uncertainty is the effect of partial or total enteral feeding and the duration of iron supplementation during infancy. The use of rhEpo in European NICUs is still generally restrictive despite some evidence of rhEpo's beneficial effects, especially in comparison with the harm of RBC transfusions. An international consensus guideline on the use of rhEpo/ESA that considers also RCTs published after the latest Cochrane meta-analysis,[4,11] such as PENUT and EpoRepair,[33,51] is required. ■

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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Data Statement

Data sharing statement available at www.jpeds.com.

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