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Consensus Statement | Pediatrics

Clinical Practice Guideline for Red Blood Cell Transfusion Thresholds in Very Preterm Neonates

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Abstract

IMPORTANCE Red blood cell (RBC) transfusion is a common medical intervention to treat anemia in very preterm neonates; however, best transfusion practices, such as thresholds, remain uncertain.

OBJECTIVE To develop recommendations for clinicians on the use of RBC transfusions in very preterm neonates.

EVIDENCE REVIEW An international steering committee reviewed evidence from a systematic review of 6 randomized clinical trials (RCTs) that compared high vs low hemoglobin-based or hematocrit-based transfusion thresholds. The steering committee reached consensus on certainty-of-evidence ratings and worked with a panel from stakeholder organizations on reviewing the evidence. With input from parent representatives and the stakeholder panel, the steering committee used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to develop recommendations.

FINDINGS A systematic review of 6 RCTs encompassing 3483 participants (1759 females [51.3%]; mean [SD] age range, 25.9-29.8 [1.5-3.0] weeks) was used as the basis of the recommendations. The ranges for higher hemoglobin concentration (liberal) vs lower hemoglobin concentration (restrictive) threshold study arms were similar across the trials. However, specific thresholds differed based on the severity of illness, which was defined using variable criteria in the trials. There was moderate certainty of evidence that low transfusion thresholds likely had little to no difference in important short-term and long-term outcomes. The recommended hemoglobin thresholds varied on the basis of postnatal week and respiratory support needs. At postnatal weeks 1, 2, and 3 or more, for neonates on respiratory support, the recommended thresholds were 11, 10, and 9 g/dL, respectively; for neonates on no or minimal respiratory support, the recommended thresholds were 10, 8.5, and 7 g/dL, respectively (to convert hemoglobin to grams per liter, multiply by 10.0).

CONCLUSIONS AND RELEVANCE This consensus statement recommends a restrictive RBC transfusion strategy, with moderate certainty of evidence, for preterm neonates with less than 30 weeks' gestation.

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Introduction

Anemia of multifactorial origin is a common finding in preterm neonates during intensive care.[1] Most red blood cell (RBC) transfusions to treat anemia are administered to preterm neonates at up to 30 weeks' gestation.[2,3] The decision to transfuse RBCs requires assessment of the balance between benefits and harms. Transfusions of RBCs may improve cerebral oxygenation, which has been associated with lower risk of death or neurodevelopmental impairment.[4] However, RBC transfusions

may increase risks of serious adverse effects (SAEs). Hemovigilance studies have suggested that a priori hazards of RBC transfusions are more common in infants than adults,[5,6] although underreporting of SAEs in sick neonates may be substantial.[7,8] Understanding the full benefit-harm balance for RBC transfusion in very preterm neonates is important to guide clinical decision-making.

In 2020, the 2 largest randomized clinical trials (RCTs) comparing high vs low thresholds for RBC transfusion in very preterm neonates were published (Transfusion of Prematures [TOP] trial[9] and Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants [ETTNO] trial[10]). The high (liberal) transfusion policy applies a higher hemoglobin concentration as a threshold for transfusion; by contrast, the low (restrictive) transfusion policy applies a lower hemoglobin concentration as a threshold for transfusion. A recent Association for the Advancement of Blood & Biotherapies RBC transfusion guideline provided recommendations for adults and children but not for preterm neonates.[11] Therefore, we aimed to develop recommendations for clinicians on RBC transfusions in very preterm neonates. To do so, we addressed this question: When should RBC transfusions be given to premature neonates with anemia to improve clinical outcomes, including survival and long-term neurodevelopment?

Methods

Guideline Development Process

An international steering committee was established, which included members of the Neonatal Transfusion Network in Europe and the US with expertise in the fields of neonatology (including E.D., C.D., M.C.S.-V., R.M.P.), hematology or transfusion medicine (including S.J.S.), and epidemiology (including S.F.F.-G.). The guideline development process, which started in 2021 and ended in 2023, adopted standards from the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach[12] and included input from a methodologist (G.H.G.) with experience in guideline development.

Parental values and preferences were provided by a group of parent representatives set up by the European Foundation for the Care of Newborn Infants. To enable broader applicability and implementation, the steering committee obtained input from a panel of representatives from 10 stakeholder organizations (European Society for Paediatric Research, Union of European Neonatal and Perinatal Societies, European Society of Paediatric and Neonatal Intensive Care, European branch of the Extracorporeal Life Support Organization, American Academy of Pediatrics Section on Neonatal-Perinatal Medicine, Association for the Advancement of Blood & Biotherapies, International Society of Blood Transfusion, European Hematology Association, International Collaboration for Transfusion Medicine Guidelines, and Neonatal Transfusion Network) during an online meeting held on June 7, 2023 (**Figure 1**).

Population, Intervention, Comparator, and Outcome (PICO) Questions

The PICO questions with a list of potentially relevant outcomes were developed, prioritized, and agreed on by the steering committee. The final outcomes list incorporated results of a survey of the broader Neonatal Transfusion Network membership and online discussions with parent representatives (eTable 1 in Supplement 1). Critical outcomes for decision-making were survival, short term morbidity (bronchopulmonary dysplasia [BPD], intraventricular hemorrhage [IVH], periventricular leukomalacia [PVL], retinopathy of prematurity [ROP], and necrotizing enterocolitis [NEC]), and major neurodevelopmental disability at 2 years' corrected age and at school age. Weight gain and SAEs were added as outcomes based on input from parent representatives.

Two PICO questions were developed, the first of which focused on short-term outcomes and the second on longer-term outcomes; the gestational age (GA) was initially less than 34 weeks but was revised to less than 30 weeks after review of the evidence. First, in preterm neonates with less than 30 weeks' GA (population), what are the implications of using a high transfusion threshold (intervention) compared with a low transfusion threshold (comparison) during the hospital stay for

survival, short-term morbidity (BPD, IVH, PVL, ROP, NEC), transfusion-related SAEs, and weight gain at term postmenstrual age (outcomes)? Second, in preterm neonates with less than 30 weeks' GA (population), what are the implications of using a high transfusion threshold (intervention) compared with a low transfusion threshold (comparison) for mortality and major neurodevelopmental disability at 2 years' corrected age and at school age and for social and behavioral problems at school age (outcomes)?

The steering committee was not able to make a recommendation on volume and rate of transfusion because of the limited data available. However, the committee realized that clinicians would want guidance regarding these aspects of transfusion. For that reason, a range of transfusion volumes and rates used in the RCTs and frequently reported in clinical practice was provided.

Values and Preferences

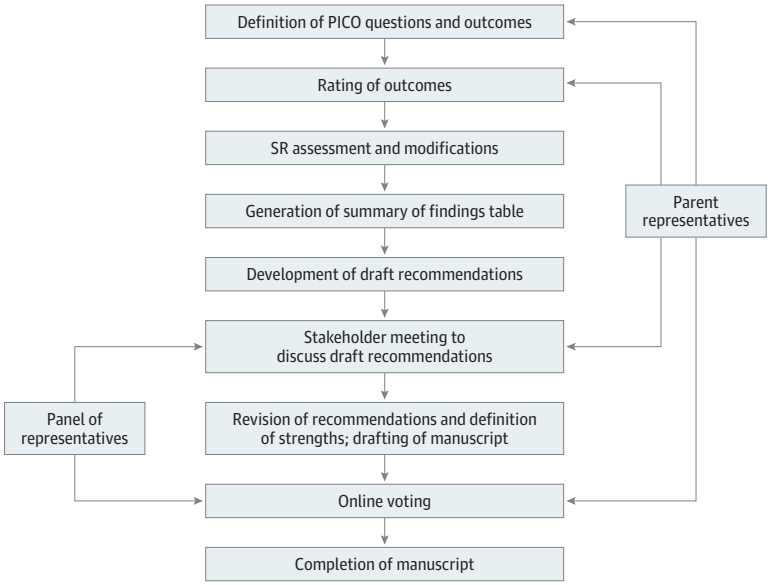
The steering committee and the broader stakeholder panel placed a high value on avoiding exposure to RBC transfusion if there was no clear evidence of benefit. There was also a preference for pragmatic guideline statements to support ease of implementation in neonatal intensive care units (NICUs), reflected in the decision to recommend single values (rather than ranges) for hemoglobin thresholds and pragmatic illness severity criteria.

Consensus Meetings

The steering committee formulated the first set of recommendations, followed by an online discussion (June 7, 2023) with the stakeholder panel. All participants disclosed any conflicts of interests, whether financial, intellectual, or personal, and were excluded from voting on related recommendations if necessary. Recommendations and a manuscript draft were shared with the stakeholder panel members, and they were asked to provide comments and vote. All stakeholder panel members agreed with the recommendations.

The steering committee developed the recommendations according to GRADE practice. A strong recommendation indicates that, most of the time, a fully informed parent would choose the given recommendation and, in general, a clinician would need a compelling reason to not follow the recommendation. A conditional recommendation indicates that, while most parents would desire the given recommendation, many would not due to variability in individual values, preferences, and

Figure 1. Flowchart of the Guideline Development Process



PICO indicates Population, Intervention, Comparator, and Outcome; SR, systematic review.

resources. For conditional recommendations, careful consideration of individual patient factors is necessary, and practice may vary.

Evidence Review and Grading

Recommendations were developed based on a systematic review[13] of transfusion thresholds in very-low-birth-weight neonates, after several assessments of its certainty were performed, including ensuring it was registered in PROSPERO, followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline, used a search strategy with key trials, and included risk-of-bias assessments. We followed the Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument for this consensus statement. As part of this effort, and following input by the stakeholder panel, the steering committee reconsidered the certainty of evidence for outcomes and rated the certainty of evidence down by 1 level for some outcomes. An asymmetric CI for PVL was also identified and confirmed by generating a random-effects model in RevMan Web (The Cochrane Collaboration) due to no PVL events in the low arm of the Bell et al[14] trial. In addition, the absolute risk per 1000 neonates for all outcomes was verified using the original trials' source data.

Evidence summaries were created for each PICO question (**Table 1**; eTable 1 in Supplement 1). With GRADE as an example, absolute effect sizes and 95% CIs were inspected to see if they crossed thresholds relevant to clinical decision-making. Additionally, relative effect sizes were reported. The effect sizes were considered in relation to the importance and frequency of the outcomes. Outcomes that were not critical for decision-making (eg, weight gain, adverse events, and outcomes at school age) or not synthesized in the systematic review were included in narrative summaries (eMethods in Supplement 1).

Rating Certainty of Evidence and Making Recommendations

The steering committee came to consensus on certainty-of-evidence ratings (Table 1) after extensive discussions with the stakeholder panel on how to rate the certainty of the trials given the relatively wide CIs and how to balance potential benefits and harms (Table 1). For many outcomes, the boundaries of CIs crossed thresholds of important differences in outcomes. For example, the CI for PVL ranged from 31 fewer events to 43 more events per 1000 in the low threshold group, and the CI

Table 1. Summary of Findings

Outcome (time frame)	Study results and measurements	No. of patients		Absolute effect size (95% CI)	Certainty (quality) of evidence
		High threshold	Low threshold		
Survival (overall)	RR: 0.99 (95% CI, 0.84-1.17); based on data from 3325 patients in 5 RCTs	139 per 1000	141 per 1000	1 fewer per 1000 (from 23 fewer to 24 greater)	Moderate, due to imprecision
Survival (up to 2 y corrected age)	RR: 0.99 (95% CI, 0.83-1.17); based on data from 3186 patients in 3 RCTs	141 per 1000	145 per 1000	1 fewer per 1000 (from 25 fewer to 25 greater)	Moderate, due to imprecision
BPD	RR: 0.96 (95% CI, 0.90-1.03); based on data from 3034 patients in 5 RCTs	462 per 1000	481 per 1000	19 fewer per 1000 (from 48 fewer to 14 greater)	Moderate, due to imprecision
Severe IVH	RR: 0.79 (95% CI, 0.53-1.17); based on data from 1146 patients in 3 RCTs	70 per 1000	89 per 1000	19 fewer per 1000 (from 42 fewer to 15 greater)	Moderate, due to imprecision
PVL	RR: 0.80 (95% CI, 0.33-1.93); based on data from 1547 patients in 3 RCTs	37 per 1000	46 per 1000	9 fewer per 1000 (from 31 fewer to 43 greater)	Low, due to serious imprecision
Severe ROP	RR: 0.88 (95% CI, 0.75-1.03); based on data from 3054 patients in 5 RCTs	156 per 1000	177 per 1000	21 fewer per 1000 (from 44 fewer to 5 greater)	Moderate, due to imprecision
NEC	RR: 0.99 (95% CI, 0.84-1.16); based on data from 3346 patients in 5 RCTs	140 per 1000	141 per 1000	1 fewer per 1000 (from 23 fewer to 23 greater)	Moderate, due to imprecision
Death or NDI (at 2 y corrected age)	RR: 1.01 (95% CI, 0.93-1.09); based on data from 3041 patients in 3 RCTs	470 per 1000	468 per 1000	5 higher per 1000 (from 20 fewer to 38 higher)	Moderate, due to imprecision

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NDI, neurodevelopmental impairment; PVL, periventricular leukomalacia; RCT, randomized clinical trial; ROP, retinopathy of prematurity; RR, relative risk.

around the best estimate of mortality or neurodevelopmental impairment included a 4% increase and a 3% decrease (**Figure 2**). Considering this uncertainty, we downrated many outcomes for imprecision based on GRADE Guidance 34.[15]

In moving from evidence to recommendations, the group considered criteria in GRADE's evidence-to-decision framework. The steering committee came to consensus on all recommendations. These recommendations may not apply to patients with acute decompensation or acute bleeding. Clinicians should consider higher thresholds for patients with sepsis or NEC, neonates requiring vasopressor or inotropic support, or patients with previous intrauterine or postnatal exchange transfusion. Additionally, these recommendations may not apply to newborns receiving erythropoiesis-stimulating agents since they were excluded in evaluated RCTs.

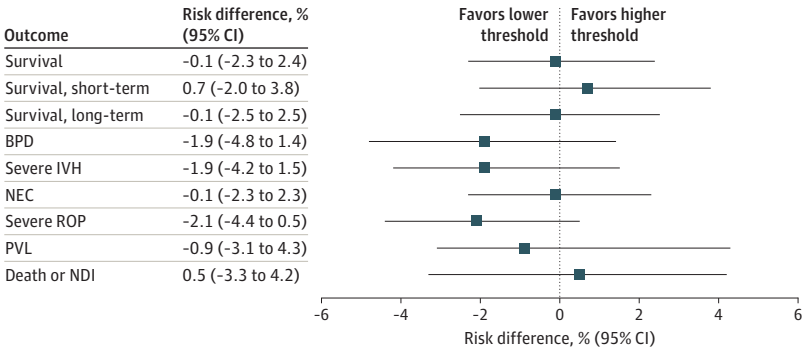
Results

A systematic review of 6 RCTs[9,10,14,16-18] involving 3483 participants (1759 females [51.3%], 1668 males [48.7%]; mean [SD] age range, 25.9-29.8 [1.5-3.0] weeks) was evaluated. These trials compared high vs low hemoglobin-based or hematocrit-based thresholds for transfusion.

Recommendations

In preterm neonates with less than 30 weeks' GA, we recommend a restrictive RBC transfusion strategy; that is, transfusion when the hemoglobin concentration is as shown in **Table 2** (conditional recommendation, with moderate certainty of evidence). The recommended hemoglobin thresholds varied on the basis of postnatal week and respiratory support needs. At postnatal weeks 1, 2, and 3 or more, for neonates on respiratory support (nasal cannula flow rate of ≥1 L/min, any positive airway pressure) the recommended thresholds were 11, 10, and 9 g/dL, respectively; for neonates on no or minimal respiratory support, the recommended thresholds were 10, 8.5, and 7 g/dL, respectively (Table 2); to convert hemoglobin to grams per liter, multiply by 10.0.

Figure 2. Forest Plot Summary of Pooled Estimates From Trials



Risk estimates from Table 1, with asymmetric CI for periventricular leukomalacia (PVL) based on relative risk estimates in Table 1. Squares represent point estimates. BPD indicates bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NDI, neurodevelopmental impairment; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Table 2. Recommendations

Transfusion threshold	Respiratory support[a]	No or minimal respiratory support
Hemoglobin-based threshold, g/dL		
Postnatal wk 1	11	10
Postnatal wk 2	10	8.5
≥Postnatal wk 3	9	7
Hematocrit-based threshold, %[b]		
Postnatal wk 1	33	30
Postnatal wk 2	30	25
≥Postnatal wk 3	27	21

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0; hematocrit to proportion of 1.0, multiply by 0.01.

[a] Respiratory support was defined as invasive mechanical ventilation, continuous positive airway pressure or noninvasive intermittent positive pressure ventilation, or nasal cannula flow rate of 1 L/min or greater.

[b] Hematocrit thresholds, provided for ease of implementation, were calculated by multiplying the hemoglobin level by 3.

Based on the RCTs considered for this recommendation and recent observational studies, we provided information on frequently used volumes and durations of RBC administration. However, these data were not part of the initial PICO questions for this guideline; therefore, no specific recommendations are provided.

Evidence Summary

In the RCTs considered in the systematic review on which this RBC transfusion strategy recommendation was based, ranges for high vs low threshold study arms were similar[13] (eTable 2 in Supplement 1). However, specific thresholds differed by the severity of illness, which was defined using variable criteria. For the first PICO question regarding short-term outcomes, a low threshold compared with a high threshold had little or no association with survival at any time point (risk difference [RD], −0.1% [95% CI, −2.3% to 2.4%]; relative risk [RR], 0.99 [95% CI, 0.84-1.17]; based on 5 trials,[9,10,14,17,18] except for the trial by Blank et al[16], which did not report mortality, with 3325 patients [with moderate certainty of evidence]). Similarly, there was little to no association with survival up to 2 years, BPD, severe IVH (grade 3-4), severe ROP (grade ≥3), or NEC (with moderate certainty of evidence) (Table 1). For the outcome of PVL, a low threshold compared with a high threshold probably had little or no association (with low certainty of evidence due to very serious imprecision).

For death or neurodevelopmental impairment at 2 years' corrected age, there was little or no difference between low and high thresholds (RD, 0.5% [95% CI, −2.0% to 3.8%]; RR, 1.01 [95% CI, 0.93-1.09]; based on 3 trials[9,10,18] with 3041 patients [with moderate certainty of evidence]) (Figure 2). Studies reporting on outcome at school age are ongoing from the National Institute of Child Health and Human Development Neonatal Research Network.

Several small RCTs have assessed the association of transfusion volume with various clinical outcomes. However, none of these trials was powered to assess relevant clinical outcomes, such as mortality, long-term neurodevelopmental outcome, or substantial morbidities. Additionally, not all trials have assessed the need for follow-up transfusions. Volumes compared in dose-effect trials were between 10 and 20 mL/kg (eMethods in Supplement 1). The volumes used in previous RCTs comparing low and high thresholds were 10 mL/kg,[17] 15 mL/kg (including the TOP trial),[9,14,18] and 20 mL/kg (ETTNO trial).[10]

A large recent survey of 343 NICUs from 18 European countries found that RBC transfusion volumes ranged between 10 and 20 mL/kg, with outliers at 25 and 30 mL/kg.[19] The median (IQR) transfusion duration was 4 (3-4) hours.[19]

Subgroup Analyses

In the systematic review, subgroup analyses evaluated all-cause mortality by birth weight (<1000 g vs >1000 g), GA (<28 weeks vs ≥28 weeks), sex (male vs female), and transfusion volume (<20 mL/kg vs ≥20 mL/kg).[13] The systematic review reported no compelling evidence of any subgroup differences.

Rationale for Recommendations

The recommendation for the low threshold was based on consistent evidence from multiple RCTs addressing both PICO questions that showed little or no benefits of a high threshold (moderate certainty) on the short term and 2-year outcomes reported. However, we acknowledge that studies of school-age children are ongoing, and recommendations may need to be reconsidered when data become available. Given the population of newborns enrolled in the RCTs, the steering committee specified the relevant population as neonates with less than 30 weeks' gestation. The values and preferences of both clinicians and families were also considered in favor of avoiding potential adverse effects associated with RBC transfusions in the absence of clear evidence of benefit. However, these recommendations may not apply to every patient, such as those with acute or severe illness. They also reflect the best currently available evidence but might change in the future depending on new evidence (eg, follow-up studies of school-age children).

In the process of developing this guideline, the steering committee made multiple decisions to formulate the recommended transfusion thresholds. First, because the TOP and ETTNO trials were the largest contemporary trials and most likely to inform best practice, the steering committee based the definition of transfusion thresholds on the most recent TOP and ETTNO trials. The present recommendations were consistent with those in a prior Cochrane review.[20] Second, the definitions for higher level of illness severity (any respiratory support or critical state of health) were unified because they differed among the trials. After discussion, for simplicity reasons, the steering committee defined higher level of illness severity as requiring mechanical ventilation, continuous positive airway pressure or noninvasive intermittent positive pressure ventilation, or nasal cannula flow rate of 1 L/min or greater. A substantial number of infants in the TOP and ETTNO trials were categorized as having any respiratory support or being critically ill and therefore received transfusions at higher thresholds. Some of these infants would be still assigned to higher thresholds after the present recommendations. This decision was made to avoid recommending lower thresholds than those actually tested in the RCTs.

Third, hemoglobin concentration was selected as the preferred laboratory measure for transfusion threshold because hemoglobin may be a more relevant measure (although surrogate marker) of blood oxygenation capacity. However, converted hematocrit thresholds are provided to facilitate guideline implementation. Fourth, additional studies may be needed to identify the risks and benefits of transfusion at hemoglobin values lower than those tested in the trials, particularly given the concerns about severe anemia raised in prior observational studies (ie, risk of NEC[20]).

Discussion

The guideline herein provides recommendations for restrictive RBC transfusion strategies in preterm neonates with anemia born at less than 30 weeks' GA. This guideline involved a broad group of stakeholders, including parents and field experts, and provides an algorithm for transfusion support that can be readily applied in NICUs.

The rationale for a restrictive threshold recommendation incorporates the high value placed on avoiding transfusions when there is no clear evidence of benefit. There is a need for caution when assuming the benefits of RBC transfusion in the absence of data, as was highlighted in the PlaNeT-2 MATISSE (Platelets for Neonatal Transfusion-2/Managing Thrombocytopenia in a Special Subgroup) trial, which showed unexpected harm associated with platelet transfusions.[21] It is also important to recognize that the safety of tolerating anemia below the levels studied in previous RCTs[9,10,14,16-18] is uncertain. The algorithm presented here is simple to apply and audit, but clinicians should incorporate clinical assessments into any transfusion decision.

There is a need to address the effective implementation of this guideline given the poor uptake of evidence-based recommendations. Clinical transfusion practice was described in a European survey and an American observational cohort study.[2,19] The thresholds recommended in the TOP and ETTNO trials underlying this guideline span pretransfusion hematologic values used routinely in a cohort of US NICUs, suggesting they are within the ranges of routine practice. Importantly, some European NICUs reported using thresholds lower than those recommended by this guideline and sometimes lower than those tested in the TOP and ETTNO trials. It is, therefore, likely that adoption of these guidelines will play a role in changes in transfusion practices at many NICUs and will need to be supported by implementation and follow-up studies.

Strengths and Limitations

This guideline has several strengths. The steering committee included experts on issues associated with blood product use in critically ill neonates. Recommendations were based on systematic reviews of the literature using the GRADE approach.[22] Parents were consulted in a parallel process to inform the values and preferences underlying the recommendations, which were made explicit.

The guideline also has limitations. First, despite previous trials with low risk of bias, some uncertainty remained, as reflected in the CIs crossing clinically significant differences in mortality and morbidity rates, which resulted in ratings of moderate and not high certainty of evidence. Second, there were substantial differences in definitions of critical illness and RBC transfusion volumes between the 2 recent trials,[9,10] which made it difficult to simply merge them into 1 transfusion strategy. All trials were unblinded, which potentially could lead to bias from differential cointerventions between study arms. Third, the recommendations are not yet supported by longer-term outcomes, such as school-age implications of differing transfusion thresholds. Long-term outcomes are particularly important because iron-deficiency anemia in infancy is associated with more subtle cognitive, behavioral, and processing deficits that may become more evident later in life.[23] Long-term follow-up of the children enrolled in the TOP and ETTNO trials should address these concerns. Fourth, product specifications were not reported in detail in the RCTs and may not be considered by clinicians prescribing these transfusions; the implications of these characteristics have not been fully explored.[24,25] Thus, the evidence is evolving, and the recommendations will need to be updated when new relevant data are published. While we declared all conflicts of interest and did not consider any to materially affect the guideline, we selected stakeholder panel members without consideration of any financial or nonfinancial conflicts of interest.[12,26]

During the development of this guideline, the steering committee recognized that the transfusion volumes (mL per kg) and rates (mL per hour) varied between the RCTs (eMethods in Supplement 1). Volume and rate could affect the risk for related adverse outcomes, such as transfusion-associated volume overload or lung injury, both likely underdiagnosed in critically ill preterm infants.[7] This area is where further research is desired. We also did not consider different blood banking practices. Other areas in need of research include patient blood management, including delayed cord clamping and limiting unnecessary blood sampling to prevent iatrogenic anemia as well as iron supplementation.

Conclusions

This consensus statement reports on development of a guideline by an international steering committee that recommends the use of a restrictive transfusion strategy in preterm neonates based on the best available evidence. The steering committee recognizes important additional clinical considerations, including clinical status, comorbid conditions, and parental values and preferences. This recommendation is conditional based on moderate certainty of evidence. Parents should be properly informed about the complexity of neonatal transfusion medicine, including the known benefits of transfusion, and the remaining uncertainties and unanswered questions. Given these uncertainties, parental views and preferences should be considered in the decision-making process.

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Author Contributions: Drs. Deschmann and Patel had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Patel and Stanworth equally contributed.

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Statistical analysis: Guyatt, Patel, Stanworth.

Administrative, technical, or material support: Deschmann, Dame, Sola-Visner, Stanworth.

Supervision: Dame, Sola-Visner, Patel, Stanworth.

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Group Information: The members of the Neonatal Transfusion Network are listed in Supplement 2.

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SUPPLEMENT 1.

eTable 1. Summary of PICO Questions
eMethods. Outcomes of Interest Not Addressed by the Systematic Review
eTable 2. PICO Questions Addressed in the Six Red Blood Cell Transfusion Trials
eReferences

SUPPLEMENT 2.

Nonauthor Collaborators